Neurofeedback in Children with ADHD

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Behavioral and neurocognitive treatment results post-intervention and at follow-up

Katleen Geladé

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Chapter 1

General introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common childhood-onset developmental disorders[1] characterized by age-inappropriate levels of inattention, hyperactivity and impulsivity.[2] ADHD affects quality of life in several domains, interfering with interpersonal, emotional, cognitive and academic functioning.[3] The overall prevalence of ADHD in children is estimated at 5.9 percent.[4] Symptom persistence of ADHD in adulthood is difficult to measure as it depends highly on how it is measured, variability in sources (between informants, cognitive-neuropsychological and neurophysiological data), and symptom thresholds used to define ADHD persistence.[5-7] Nevertheless, the most recent follow-up of the National Institute of Mental Health Collaborative Multisite Multimodel Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (MTA), revealed significant persistence of the disorder demonstrated by higher levels of symptom severity in adulthood in the ADHD group compared to the local normative comparison group.[8]

Stimulant medication is a widely used and effective intervention for children with ADHD.[9] Methylphenidate is the most commonly prescribed stimulant. The medication is supposed to act by blocking dopamine and norepinephrine reuptake, thereby restoring deficient catecholamine levels leading to a decrease of ADHD symptoms.[10] There has been a substantial worldwide increase in the prescription rates of methylphenidate and other medications for patients with ADHD over the last decade.[11-13] However, many parents are reluctant to accept medication for their child.[14] Moreover, side effects[15] and the lack of evidence for long-term effects16 have led to the search for alternative treatments for ADHD.

Neurofeedback has been proposed as a promising non-pharmacological treatment for ADHD.[17,18] The treatment is thought to operate by the principles of operant learning. The patient learns to modify brain activity using visual and/or auditory feedback of electroencephalogram (EEG) activity. By learning the patient to adapt brain activity using real-time feedback, neurofeedback aims to teach how specific cortical frequencies can be controlled. The applicability of neurofeedback in humans was first discovered in patients with epilepsy.[19] Soon after that discovery, in 1976, Lubar & Shouse described the first case study of neurofeedback training in a hyperkinetic child. In the last decade, there has been an increase of research into neurofeedback in ADHD. Nevertheless, results of meta-analyses on the efficacy of neurofeedback in children with ADHD are inconsistent.[20-23]

The first aim of this thesis is to investigate behavioral **(chapter 2)** and neurocognitive **(chapter 3)** effects of neurofeedback compared to stimulant medication, and physical activity, as a semi-active control condition, in children with ADHD at post-intervention and six-month

naturalistic follow-up **(chapter 4)**. The second aim of this thesis is to investigate possible underlying working mechanisms of neurofeedback. To explore whether the effects induced by neurofeedback are specifically mediated by altered brain function, we compared neurophysiological outcome measures of neurofeedback to stimulant medication and physical activity at six-month follow-up **(chapter 5)**. In addition, to get a better understanding of learning in neurofeedback, we explore the ability to learn from feedback in children with ADHD **(chapter 6)**.

Neurofeedback for ADHD

The sensorimotor rhythm (SMR) (13-15 Hz) protocol, a frequency training, was used in the first study describing the successful reduction of hyperactivity induced by neurofeedback in a hyperkinetic child.[24] After these encouraging findings, more research was conducted on the application of neurofeedback in therapeutic settings.[25-28] Nowadays, two types of neurofeedback training can be distinguished: slow cortical potential (SCP) training and frequency training. Both protocols make use of real-time feedback on brain activity to learn the child how to voluntary switch to the desirable states. The SCP training targets the presumed impaired excitation thresholds in ADHD.[29] SCP training in ADHD focuses on regulation of cortical excitability to enhance contingent negative variation (CNV) which has been reported to be associated with reduced ADHD symptomatology.[29-31] The most examined type of neurofeedback training[32] in children with ADHD is the frequency band training. Children with ADHD have been found to show increased theta (4-7Hz) and decreased beta activity (13-20Hz) compared to typically developing (TD) children.[33] These altered EEG frequency bands have been associated with lower vigilance and reduced attention, respectively.[34] Therefore, an often used frequency band protocol in ADHD is the theta/beta protocol, repressing theta and reinforcing beta at the vertex.[32]

ADHD diagnosis is based on the observation of behavioral symptoms, inattention and/or hyperactivity/impulsivity, in everyday activities. Therefore, most studies evaluating the efficacy of neurofeedback investigated behavioral change after neurofeedback training. Meta-analyses on behavioral outcome measures rated by parents and teachers in children with ADHD found inconsistent results, with conclusions ranging from neurofeedback being a non-effective treatment as assessed with blinded assessments,[21,23] to neurofeedback being more efficacious than active control conditions,[22] to neurofeedback generating durable treatment effects for at least 6 months after treatment.[35] Similar inconsistent results, although less intensively investigated than behavioral outcomes, were found in neurocognitive outcome measures.[36-40] In addition, long-term follow-up effects of neurofeedback, exploring the maintenance and/or possible delayed effects of

neurofeedback, are scarce and again results are mixed.[41-45] These mixed findings might be due to divergent methodologies and research designs used in these studies in terms of (1) random allocation of participants, (2) controlling for concomitant treatments and/or non-specific treatment effects, and (3) the use of blinded assessment of treatment effects.[17]

In sum, neurofeedback is a potentially effective treatment for behavioral and neurocognitive symptoms in ADHD. However, results on both short-term and long-term effects of neurofeedback are mixed. In the current thesis, we compared neurofeedback to both stimulant medication and a physical activity intervention. Physical activity could be another treatment approach for ADHD that utilizes protective effects of exercise on brain functioning.[46,47] However, beneficial effects of chronic exercise in children with ADHD are preliminary and have yet to be established in randomized controlled trials.[48] In the current thesis, physical activity was applied as a semi-active control condition to control for non-specific effects, such as parental engagement and personal attention. Therefore, neurofeedback and physical activity training were matched on duration and intensity. The aim of **chapter 2** is to compare the effects of neurofeedback, as a stand-alone intervention, to an optimal dose of methylphenidate and physical activity, semi-active control group to control for non-specific treatment effects, in children with ADHD. In **chapter 3** the three treatments will be compared on the effects of neurocognitive functioning. In **chapter 4** of this thesis we will study long-term behavioral and neurocognitive effects of neurofeedback to stimulant medication, and a semi-active control group.

Mechanisms underlying neurofeedback

To get more insight into underlying working mechanisms of neurofeedback, it has been suggested to investigate, amongst others, sustainable EEG changes induced by neurofeedback. In addition, it has been recommended to identify the relation between these EEG changes and clinical outcomes in children with ADHD.[49] Results of randomized controlled trial (RCT) studies investigating sustainable effects of neurofeedback on power spectra by evaluating effects from pre- to post-intervention are mixed.[42,50] The RCT study of Ogrim and Hestad[50] comparing neurofeedback and stimulant medication, found no changes in power spectra in either intervention. In contrast, Gevensleben et al.[42] found a decrease in theta power in children that received neurofeedback compared to a control intervention. Note that these studies all described results found at post-intervention. To assess sustainability of EEG changes after neurofeedback training, it is of utmost importance to evaluate long-term effects of EEG changes. To our knowledge there are no follow-up studies on RCT's that provide insight into possible long-term effects of neurofeedback on EEG

power spectra. Therefore, long-term effects of neurofeedback on EEG power spectra should be explored. The aim of **chapter 5** is to explore whether neurofeedback can induce long-term effects on EEG power spectra compared to stimulant medication and physical activity.

The aim of neurofeedback is for the patient to learn to modify brain activity using visual and/or auditory feedback of EEG activity. However, instrumental learning, the ability to change behavior in response to positive and negative feedback, is thought to be impaired in children with ADHD. Neurobiological models of ADHD suggest a deficiency in reinforcement learning due to altered levels and/or activity of striatal dopamine.[51-54] Although, these models differ in level of explanation[55], they all agree on the prediction that children with ADHD show poor reinforcement learning compared to controls, particularly when reinforcement is not delivered consistently and frequently.[51-54] Experimental studies that manipulated the consistency of reinforcement delivery to investigate this prediction for individuals with ADHD, however, showed inconsistent results.[54,56-58] To get more insight into learning in neurofeedback, the aim of **chapter 6** is to examine instrumental learning, particularly when feedback is not consistent, in children with ADHD compared to TD children.

Study design

Results reported in this thesis were based on data from a large RCT (ClinicalTrials.gov identifier: NCT01363544), conducted between September 2010 and January 2015. The aim of this randomized controlled multicentre three-way parallel group study was to compare treatment effects of theta/beta neurofeedback, stimulant medication with methylphenidate and physical activity (semi-active control condition) on behavioral, cognitive and electrophysiological measures. Eligible participants were Dutch speaking children, 7-13 years with an estimated IQ $\geq$ 80, and a primary clinical DSM-IV-TR diagnosis of ADHD.[2] Before entering the study, parent and teacher ratings on the Disruptive Behavior Disorders Rating Scale (DBDRS)[60] were required to confirm a diagnosis of ADHD: i.e., at least one of the scores on the Inattention or Hyperactivity/Impulsivity scales had to be above the 90th percentile for one of the informants, and above the 70th percentile for the other informant. Furthermore, children had to be free of stimulants for at least one month prior to the intervention and were not allowed to have any diagnosed neurologic disorder. Children with ADHD were tested at pre-, post-intervention, and at six-month naturalistic follow-up.

In **chapter 6**, in which we will explore the ability to learn from feedback in children with ADHD, we also report on typically developing (TD) children. TD children, 7-13 years with an estimated IQ $\geq$ 80 and free of any psychiatric disorder, were recruited from primary schools, after school programs and sport clubs. TD children were required to obtain parent and teacher

ratings <70th percentile on both scales of the DBDRS to rule out the presence of significant ADHD symptoms. TD children performed one single measurement which was identical to the pre-intervention assessment of children with ADHD.

Thesis aims and outline

The first aim of the current thesis is to examine behavioral and neurocognitive effects of neurofeedback compared to stimulant medication and physical activity, a semi-active control group, in children with ADHD both at post-intervention and six-month naturalistic follow-up. Second, this thesis aims to investigate underlying working mechanisms of neurofeedback, neurophysiological effects of neurofeedback at six-month follow-up. In addition, this thesis aims to examine the ability to learn from feedback in children with ADHD compared to TD children.

To address the first aim of this thesis – to study the behavioral and neurocognitive effects of neurofeedback, **chapter 2** will examine behavioral change of ADHD core symptoms after neurofeedback compared to stimulant medication and physical activity rated by both parents and teachers. **Chapter 3** will investigate neurocognitive treatment effects. This chapter will focus on the effects of neurofeedback on neurocognitive outcome measures including attention, inhibition, and working memory often found to be impaired in ADHD.[61-64] **Chapter 4** will focus on the long-term, six-month follow-up, behavioral and neurocognitive treatment effects of neurofeedback compared to stimulant medication and physical activity. This study aims to explore possible delayed effects of neurofeedback. **Chapter 5** will elaborate on **chapter 4**, by exploring long-term EEG treatment effects to gain insight into the specificity and underlying working mechanisms of neurofeedback. To address the second aim of this thesis – to study the underlying working mechanisms of neurofeedback, **chapter 6** will attempt to contribute to the understanding of feedback learning in children with ADHD during neurofeedback training. In addition, generalization of learning will be explored. In **chapter 7**, a general summary and discussion of findings will be provided.

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Chapter 2

Behavioral effects of neurofeedback compared to stimulants and physical activity in ADHD: A Randomized Controlled Trial

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Abstract

Objective: The efficacy of neurofeedback (NFB) as a treatment for ADHD, and whether NFB is a viable alternative for stimulant medication, is still an intensively debated subject. The current randomized controlled trial (RCT) compared NFB to (1) optimally titrated methylphenidate (MPH) and (2) a semi-active control intervention, physical activity (PA), to account for non-specific effects.

Method: A multicentre three-way parallel group study with balanced randomization was conducted. Children with a DSM-IV-TR diagnosis of ADHD, aged 7-13, were randomly allocated to receive NFB (n=39), MPH (n=36), or PA (n=37) over a period of 10-12 weeks. NFB comprised theta/beta training on the vertex (Cz). PA consisted of moderate to vigorous intensity exercises. NFB and PA were balanced in terms of number (~30) and duration of sessions. A double-blind pseudo randomized placebo-controlled cross-over titration procedure was used to determine an optimal dose in the MPH intervention. Parent and teacher ratings on Strength and Difficulty Questionnaire (SDQ) and Strengths and Weaknesses of ADHD symptoms and Normal behavior scale (SWAN) were used to assess intervention outcomes. Data collection took place between September 2010 and March 2014.

Results: Intention-to-treat analyses revealed an improvement on parents reported behavior on the SDQ and SWAN hyperactivity/impulsivity scale, irrespective of received intervention [η_p^2=0.21-0.22, $p \leq .001$], whereas the SWAN inattention scale revealed more improvement in children who received MPH than NFB and PA [η_p^2=0.13, $p \leq .001$]. Teachers reported a decrease of ADHD symptoms on all measures for MPH, but not for NFB or PA [range of η_p^2=0.14-0.29, $p \leq .001$].

Conclusions: The current study found that optimally titrated MPH is superior to NFB and PA in decreasing ADHD symptoms in children with ADHD.

Introduction

Attention-deficit/hyperactivity disorder (ADHD)[1] is one of the most common childhood neurodevelopmental disorders.[2] Stimulant medication is a widely used and effective intervention for ADHD.[3] However, several limitations have been reported, including a substantial group that fails to show improvement and adverse side effects such as sleeping problems, decreased appetite, and headaches.[4] Furthermore, there is limited evidence for long-term effects of stimulant treatment.[5] As a result, there is demand for alternative interventions for ADHD.

Neurofeedback has been proposed as a promising non-pharmacological intervention for ADHD.[6,7] The aim of neurofeedback is to alter brain activity patterns by providing the patient with visual or auditory feedback on electroencephalogram (EEG) activity. Alterations in brain activity patterns have been associated with behavioral problems as seen in ADHD.[8,9] Compared to typically developing children, children with ADHD show increased theta (4-7Hz) and decreased beta activity (13-20Hz).[8] Greater theta activity is related to poor vigilance, whereas greater beta activity is related to enhanced attention.[9] Accordingly, the most widely studied neurofeedback treatment protocol for ADHD aims at decreasing theta and increasing beta activity at the vertex (Cz).[7] However, more recent studies question the association between increased theta/beta ratio and ADHD.[10] Comorbid disorders might have a mediating effect on the theta/beta ratio.[10,11] Meta-analyses evaluating the effects of neurofeedback in children with ADHD are inconclusive, with conclusions ranging from neurofeedback being a non-effective treatment as assessed with blinded assessments,[12] to neurofeedback being more efficacious than active control conditions,[13] to neurofeedback being a 'efficacious and specific' treatment.[14] Inconsistent results might be due to differences between studies in terms of (1) random allocation of participants, (2) controlling for concomitant treatments and/or non-specific treatment effects, and (3) the use of blinded assessment of treatment effects.[6]

Results of randomized controlled trial (RCT) studies comparing the effects of neurofeedback and stimulant medication in children with ADHD are mixed. Two out of three RCTs showed that neurofeedback is as effective as stimulant medication,[15,16] with the third study[17] showing superior effects for medication compared to neurofeedback on ADHD symptoms. Mixed findings across studies may be the result of varying protocols for both neurofeedback and medication interventions.

In the current study, we compared neurofeedback to both stimulant medication and a physical activity (PA) intervention. Physical activity could be another treatment approach for ADHD that utilizes protective effects of exercise on brain functioning.[18] However, beneficial

effects of chronic exercise in children with ADHD are preliminary and have yet to be established in randomized controlled trials.[19] In the current study, PA was applied as a semi-active control condition to control for non-specific effects, such as parental engagement and personal attention. Therefore, neurofeedback and physical activity training were matched on duration and intensity. The aim of the present RCT study was to compare the effects of neurofeedback (NFB) with (1) stimulant medication (MPH) and (2) physical activity (PA) as semi-active control condition in children with ADHD.

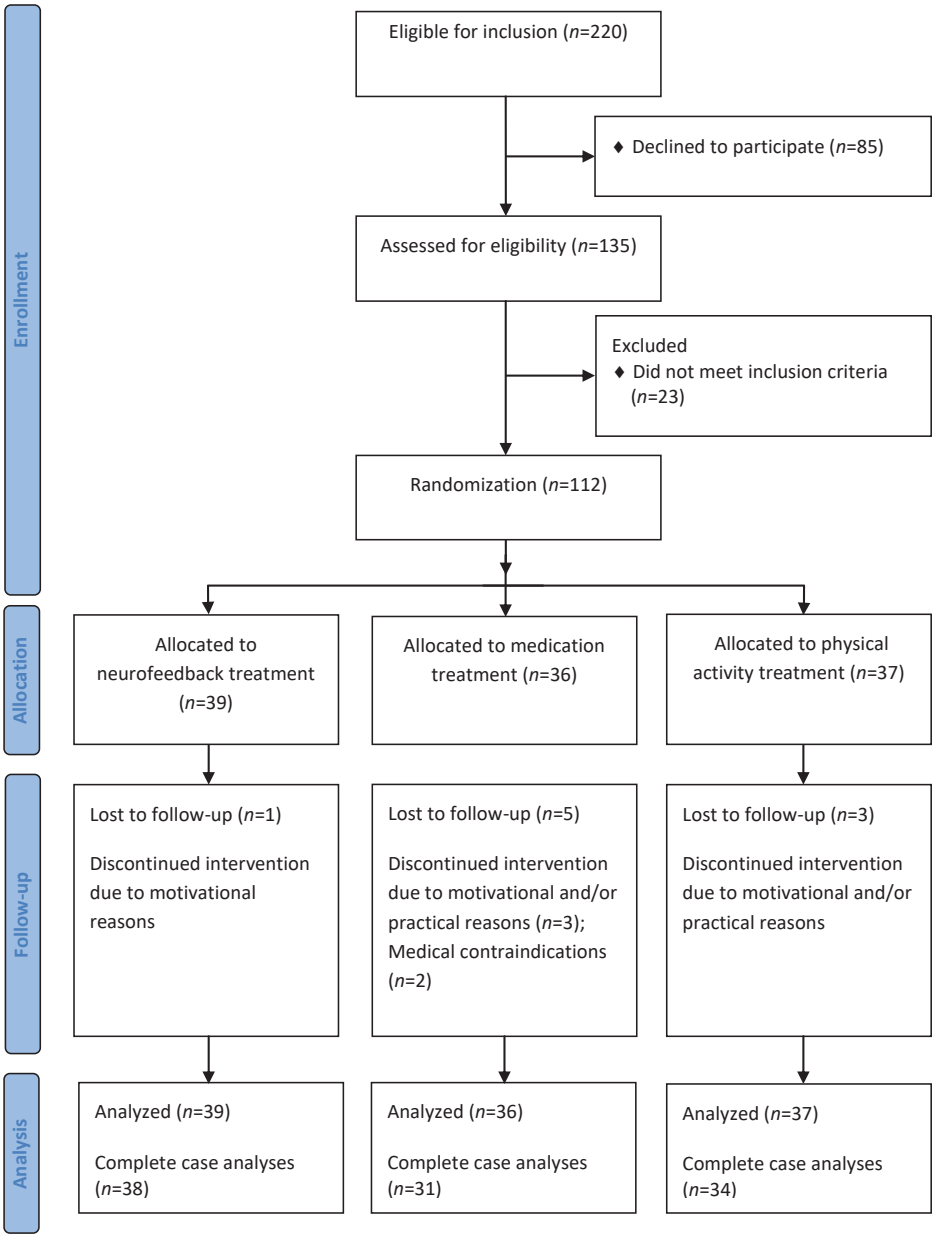
Methods

Participants

Eligible participants were Dutch speaking children, 7-13 years, with a primary clinical DSM-IV-TR diagnosis of ADHD.[1] Children with ADHD were recruited from fifteen child mental health outpatient care facilities in the West of the Netherlands. Before entering the study, parent- and teacher ratings on the Disruptive Behavior Disorders Rating Scale (DBDRS)[20] confirmed their diagnosis; at least one of the scores on the Inattention or Hyperactivity/Impulsivity scales had to be above the 90th percentile for one of the informants, and above the 70th percentile for the other informant. At study entry, all children were free of stimulant use for at least one month. Exclusion criteria were neurological disorders and IQ below 80 as measured by a four subtest version of the Wechsler Intelligence Scale of Children-III (WISC-III) including the subtests Vocabulary, Arithmetic, Block Design, and Picture Arrangement.[21] No restrictions were set on other comorbidities. Comorbid disorders were diagnosed according to DSM-IV-TR and retrieved from the medical records. Comorbid disorders included learning disorders (NFB; n=5, MPH; n=2, PA; n=1), autism spectrum disorders, (NFB; n=3, MPH; n=2, PA; n=3), anxiety disorders (NFB; n=2, MPH; n=0, PA; n=2), and mood disorder (NFB; n=1, MPH; n=0, PA; n=0). Chi-square test revealed no significant difference in the distribution of comorbid disorders over groups (χ^2 (8, N=112)=12.88, p=.12).

Initially, 112 children with ADHD were randomized over the three interventions, with 103 children completing their intervention. Figure 1 presents a flow diagram of participants.

Figure 1. Flow diagram randomized controlled trial.



Trial design

A multicentre three-way parallel group study with balanced randomization was conducted. A randomization table was created using a computerized random number generator.22 Stocks of nine unmarked sealed envelopes were presented to parents at intake. Parents randomly picked an envelope revealing intervention allocation. Subsequently, children, parents, and teachers were aware of the allocated group. Data collection took place between September 2010 and March 2014.

To detect a medium effect size (f=0.25) for three groups to be sufficient in a repeated measures (RM) analysis of variance (ANOVA) with an alpha 0.05 and a power of 95%, using G*power version 3.1.5,23 a total sample size of 66 (i.e. 22 per group) was calculated. In case of two groups, to perform relevant post-hoc analysis, a total sample size of 54 (i.e. 27 per group) was calculated to detect a medium effect size (f=0.25) in a RM ANOVA with an alpha 0.05 and a power of 95%. In the current study, the smallest group size was 29. Consequently, all groups had enough participants to the detect a medium effect size. This report complies with the CONSORT 2010 guidelines for reporting parallel group randomized trials.24 The trial was registered on clinicaltiral.gov (Ref. No. NCT01363544).

Interventions

NFB and PA interventions consisted of three individual training sessions a week, with each session lasting 45 minutes including 20 minutes of effective training, over a period of 10-12 weeks.

Neurofeedback. Theta/beta training was applied with the aim to inhibit theta (4-8Hz) and reinforce beta (13-20Hz) activity at Cz. The mean number of training sessions of participants who completed the assessments at post intervention (n=38) was 29 (M = 28.53, SD = 2.63, range between 19-30). Theta/beta index was represented to the participant by simple graphics on a screen. Successful reduction of the theta/beta index as averaged over one trial relative to session baseline, was rewarded with the appearance of a sun and granted with credits. To promote generalization of the learned strategies into daily life, transfer trials were used. Transfer trials were presented without immediate visual feedback and were included from session 11 (25%) and session 21 (50%) onwards. To further transfer learned behaviors, participants were instructed to retrieve their neurofeedback experiences by watching printed graphics of the training during school and homework. Compliance was verified by questioning the participants whether they used the transfer cards over the intervention period. Transfer cards were used by 84% of the participants. See also Supplementary Appendix 1 for more detailed information about the neurofeedback intervention.

Medication. A four-week double-blind randomized placebo-controlled titration procedure was used to determine the optimal individual dose of short-acting methylphenidate (MPH).[25] The titration phase was preceded by a baseline week to determine ADHD symptoms without MPH, and was followed by a lead-in week in which on three consecutive days, twice-daily (at breakfast and lunch time), doses of (1) 5mg, (2) 10mg, and (3) 15mg (<25kg body weight) or 20mg MPH (>25kg body weight) were used to assess possible adverse effects. During the four week titration phase, children received in pseudo-random order (1) 5mg, (2) 10 mg, (3) 15mg or 20 mg MPH or (4) placebo for one week, twice daily. During the titration phase, children, parents and teacher as well as the researchers were blind with regard to the prescribed dose (placebo, 5, 10 or 15/20 mg). At the end of each week, parents and teacher were asked to evaluate inattention and hyperactivity/impulsivity symptoms on the DBDRS, and adverse effects on the MTA Side Effect Rating Scale.[26] Children were classified by a standardized procedure[27] as responders when their ADHD symptoms significantly decreased compared to placebo (n=29). The standardized procedure27 classified children as non-responders when they did not show any decrease in inattention and hyperactivity/impulsivity symptoms across MPH doses and placebo (n=2). When children were found to respond equally well across different MPH doses, the lowest MPH dose was prescribed. The two non-responders were treated with 5mg MPH twice daily. The child's psychiatrist prescribed the optimal dose for the remaining intervention period (5mg to 10 children including 8 responders and 2 non-responders, 10mg to 14 children, 15mg to 2 children, and 20mg to 5 children).

Physical activity. Maximum heart rate (HRmax) was determined before the start of the first training session using a standard maximum heart rate test. Each training session started with 5 minutes of warming up, followed by five 2-minute moderate intensity exercises at a level of 70-80% of HRmax. After a 5-minute break, five 2-minute vigorous intensity exercises of 80-100% of HRmax were performed. Each training finished with a 5-minute cool down. Time and heart rate were monitored and registered using a POLAR FT4 watch (Polar Electro Oy, Kempele, Finland). The mean number of sessions of participants who completed the assessments at post intervention (n=34) was 28 (M=27.74, SD=3.56, range 12-30).

Outcome Measures

Primary outcome measures included parent and teacher reports on the Strength and Difficulty Questionnaire (SDQ)[28,29] and the Strengths and Weaknesses of ADHD symptoms and Normal behavior scale (SWAN).[30] The Total scale of the SDQ and the SWAN scales Inattention and Hyperactivity/Impulsivity were used to assess intervention effects.

Secondary outcome measures included a custom-made expectancy scale filled out pre-intervention by parents and teachers. Quality of sleep was assessed using the total scale of the Sleep Disturbance Scale (SDSC)[31] as evaluated by parents.

Procedure

The study was approved by the national medical ethics committee (NL 31641.029.10 CCMO). Written informed consent was obtained before participation from all parents and children aged 11 years and older.

Pre-intervention assessment took place in the week prior to the start of the intervention. Post-intervention assessment took place one week after the last training. In addition to the data presented here, neuropsychological and electroencephalogram data were collected. During post-intervention assessment, the MPH-group continued use of medication at the optimal titrated dose. Interventions took place between September 2010 and March 2014.

Statistical methods

Statistical analyses were performed with IBM SPSS Statistics, version 20.0.32 Differences between intervention groups in terms of background characteristics were analyzed with a chi-square test (χ^2) or a one-way ANOVA with Tukey post-hoc analyses to compare intervention groups. Attrition analyses were performed with ANOVAs comparing the initially randomized sample to the sample that completed the interventions on group characteristics and outcome measures. At pre-intervention, teacher ratings were incomplete for 5 participants on the SDQ and SWAN. The SDSC was not available for 4 participants.

Intention-to-treat analyses were performed using imputation with Last Observation Carried Forward (LOCF). To compare intervention effects, Generalized Linear Model (GLM) repeated measures (RM) ANOVAs, with time (between pre-intervention (t0) and post-intervention(t1)) as within-subject factor and group (NFB, MPH and PA) as between-subject factor were applied. For these analyses, the adjusted difference at post-intervention (ADt1-t0) and accompanying 95% confidence interval [95%CI] are reported. Effect size are expressed in percentage of explained

variance in partial eta squared (η_p^2; small, medium, and large effects correspond to η_p^2=.01, η_p^2=.06, and η_p^2=.14 respectively).[33] In case of significant time by group interactions two-way between-groups interactions post-hoc analyses were performed separately for the between-subject factors (1) NFB and MPH, (2) MPH and PA and (3) NFB and PA with time (t0, t1) as within-subject factor. Differences on expectancies were analyzed with one-way ANOVAs. To explore the relation between expectancy and difference scores (t1-t0) of primary behavioral outcome measures, Pearson correlations were computed within groups. Only significant correlations of $p \leq .05$ were reported. Complete case analyses were performed for participants who completed pre- and post-intervention assessments. For participants who completed the intervention, all parent reported primary outcome measures were complete, however, at post-intervention teacher rating on the SDQ and the SWAN were missing for two participants and SDSC data was missing for 10 participants.

Results

Group Characteristics

At pre-intervention, group characteristics and behavioral measures did not differ between the three intervention groups (Table 1).

Table 1. Group characteristics assessed pre-intervention

	NFB (*n*=39)		MPH (*n*=36)		PA (*n*=37)		Group	
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
Age (years)	9.96	1.88	9.11	1.26	9.80	1.96	2.48	ns
IQ	100.56	13.18	101.11	14.24	97.57	12.74	0.75	ns
Gender, (M/F)	30/9		27/9		28/9		0.04[a]	ns
Parent rating								
DBDRS								
Inattention	16.56	5.10	16.33	5.65	15.81	5.26	0.20	ns
H/I	14.31	6.03	13.42	6.40	13.43	6.03	0.26	ns
Teacher rating								
DBDRS								
Inattention	15.56	5.36	17.61	6.30	15.65	5.63	1.48	ns
H/I	14.13	7.12	12.75	9.70	13.05	7.44	0.30	ns

Note. DBDRS=Disruptive Behavior Disorder rating scale; H/I=Hyperactivity/Impulsivity scale; M=Mean; SD=Standard Deviation; [a]$\chi(2)$; y=years.

Attrition Analysis

No differences were found in group characteristics and pre-intervention measures between the participants as randomized and the participants who completed the intervention.

Intention-to-treat Analyses

Primary Outcome measures. See Table 2 for the main results. Parents reported improvements on the SDQ and SWAN Hyperactivity/Impulsivity scale regardless of intervention group. For the SWAN Inattention scale there was a group by time interaction. Post-hoc analyses revealed that (1) MHP showed greater improvement over time than NFB, $F(1,73)=8.24$, $p=.005$, $\eta_p^2=0.10$, and (2) PA, $F(1,71)=15.05$, $p<.001$, $\eta_p^2=0.18$. No difference was found between (3) NFB and PA, $F(1,74)=0.99$, $p=.323$, $\eta_p^2=0.01$.

Teacher reports on the SDQ and the SWAN showed differential intervention effects in the three groups as evidenced by significant group by time interactions. On the SDQ, (1) MPH showed greater improvement than NFB, $F(1,70)=15.13$, $p<.001$, $\eta_p^2=0.18$, and (2) PA, $F(1,66)=9.94$, $p=.002$, $\eta_p^2=0.13$, (3) NFB and PA did not differ, $F(1,72)=0.80$, $p=.375$, $\eta_p^2=0.01$. Similarly, on the SWAN-Inattention scale, post-hoc analyses showed that (1) MPH displayed greater improvement over time than NFB, $F(1,70)=25.98$, $p<.001$, $\eta_p^2=0.27$, and (2) PA, $F(1,66)=32.40$, $p<.001$, $\eta_p^2=0.33$. No difference was found between (3) NFB and PA, $F(1,72)=0.13$, $p=.721$, $\eta_p^2=0.002$. Likewise, for the SWAN Hyperactivity/Impulsivity scale, post-hoc analyses indicated that (1) MPH showed greater improvement over time than NFB, $F(1,70)=9.87$, $p=.002$, $\eta_p^2=0.12$ and (2) PA, $F(1,66)=12.80$, $p=.001$, $\eta_p^2=0.16$. Again, no difference was found between (3) NFB and PA, $F(1,72)=<0.01$, $p=.98$, $\eta_p^2<0.01$.

Secondary Outcome measures. At pre-intervention, we found no differences between groups in expectancy of parents. Only NFB showed a negative correlation between parent rated expectancy and change in inattentiveness as measured by the SWAN, $r(39)=-0.36$, $p=0.02$. This result reveals that parents with higher treatment expectations of neurofeedback also rated their child as more improved in terms of inattentive symptoms. Teachers had higher expectations of medication compared to NF and PA, however this was not associated with reported changes by teachers. Quality of sleep (SDSC) did not change over time for any of the intervention groups.

Complete Case Analyses

All analyses were rerun using complete case analysis, and revealed results comparable to the intention-to-treat analysis. See also the Supplementary Table 1: Complete case analyses of outcome measures and side effects.

Table 2. Intention-to-treat analyses of outcome measures and side effects

Questionnaire			Pre-Intervention	Post-Intervention	Adjusted difference	Time			Group x Time		
		n	*M(SD)*	*M(SD)*	*M*[95% *CI*]	*F*	η_p^2	*p*	*F*	η_p^2	*p*
Parent ratings											
SDQ	NFB	39	16.90(4.54)	14.92(5.98)	-1.97[-3.32, -0.63]	29.22	0.21	<.001	1.07	0.02	.35
	MPH	36	15.64(4.23)	12.86(5.15)	-2.78[-4.14, -1.41]						
	PA	37	17.22(3.93)	15.81(4.62)	-1.41[-2.69, -0.12]						
SWAN-IN	NFB	39	1.42(0.52)	1.11(0.67)	-0.32[-0.53, -0.10]	45.70	0.30	<.001	8.30	0.13	<.001
	MPH	36	1.39(0.70)	0.61(0.83)	-0.78[-1.03, -0.53]						
	PA	37	1.28(0.70)	1.11(0.72)	-0.17[-0.37, 0.02]						
SWAN-H/I	NFB	39	1.30(0.70)	1.02(0.81)	-0.29[-0.50, -0.07]	30.61	0.22	<.001	2.30	0.04	.11
	MPH	36	1.14(0.72)	0.62(0.90)	-0.52[-0.74, -0.30]						
	PA	37	1.28(0.82)	1.07(0.80)	-0.21[-0.41, -0.01]						
Teacher ratings											
SDQ	NFB	39	14.51(4.71)	15.38(5.14)	0.87[-0.46, 2.21]	3.42	0.03	.07	9.10	0.15	<.001
	MPH	33	13.48(5.43)	10.30(6.34)	-3.18[-4.86, -1.50]						
	PA	35	15.91(5.17)	15.97(4.90)	0.06[-1.21, 1.33]						
SWAN-IN	NFB	39	1.40(0.90)	1.30(0.76)	-0.10[-0.31, 0.11]	34.76	0.25	<.001	20.82	0.29	<.001
	MPH	33	1.52(0.62)	0.57(0.79)	-0.95[-1.23, -0.68]						
	PA	35	1.38(0.69)	1.33(0.72)	-0.05[-0.23, 0.12]						
SWAN-H/I	NFB	39	1.18(0.92)	1.16(1.11)	-0.03[-0.28, 0.23]	10.64	0.09	.001	8.37	0.14	<.001
	MPH	33	0.93(1.25)	0.23(0.90)	-0.70[-1.05, -0.34]						
	PA	35	1.12(0.92)	1.10(0.94)	-0.02[-0.18, 0.13]						
Side effects											
SDSC	NFB	38	45.32(10.55)	43.16(9.45)	-2.16[-4.82, 0.51]	3.51	0.03	.06	0.53	0.01	.60
	MPH	35	45.09(9.11)	44.54(9.42)	-0.54[-2.90, 1.81]						
	PA	35	44.97(12.70)	44.94(10.98)	-1.03[-2.86, 0.80]						

Note. CI=Confidence Interval, H/I=Hyperactivity/Impulsivity scale, IN=Inattention scale; M=Mean, SD=Standard Deviation, SDSC=Sleep Disturbance Scale for Children, SDQ=Strength and Difficulty Questionnaire, SWAN=Strengths and Weaknesses in ADHD and Normal Behaviors; *df* Time: *df*(1,109) Parent ratings, *df*(1,104) Teacher ratings, *df*(1,105) Side effects; *df* Group x Time: *df*(2,109) Parent ratings, *df*(2,104) Teacher ratings, *df*(2,105) Side effects.

Discussion

The present study used a three-way parallel-randomized controlled trial design and is the first to compare behavioral effects of neurofeedback, optimally titrated stimulant medication and a semi-active control condition, physical activity, in children diagnosed with ADHD. Main results revealed that neurofeedback applied as a stand-alone intervention was less effective than stimulant medication. The behavioral effects of neurofeedback were similar to the semi-active control condition.

Parent reports revealed a superior effect of medication over neurofeedback to decrease inattention problems. Our findings are in line with the results of the RCT by Ogrim and Hestad[17] who compared the effects of neurofeedback and medication. This RCT[17] study applied a double blind titration procedure to determine an optimal dose of medication similar to the current study. However, they used two different types of stimulant medication whereas our study applied one type of stimulant medication. In contrast, two other RCTs comparing the effects of neurofeedback and stimulant medication, using weight-adjusted dosing, found similar reductions in ADHD behaviors for the two treatment approaches.[15,16] The use of disparate medication protocols might explain these discrepant findings. The superiority of the titration protocol has been supported by findings of the NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (MTA). The MTA study revealed that a titration procedure, comparable to the procedure used in the current study, established higher success rates compared to standard community care.[25]

Teachers indicated that ADHD symptoms reduced with stimulant medication. In contrast to parents, however, teachers did not report any decrease in ADHD symptoms in children who received neurofeedback or physical activity. The discrepancy between the effectiveness of the three interventions as reported by parents and teachers might be explained in terms of differences between raters in their investment in the intervention.[12] Neurofeedback and physical activity required direct involvement and devotion of parents, while teachers held more passive roles. Another possibility is that treatment expectancy of parents and teachers confounded our measures. However, only for the neurofeedback group, higher parent expectations were predictive of greater improvements on inattention symptoms. This finding suggests that the parent reported decrease of inattention problems in the neurofeedback group may be (partly) explained by parental expectations.

Sleep quality was not affected by any of the received interventions. This is remarkable, since sleep disturbances are one of the most common reported side effects of stimulant medication

use.[34,35] However, in our study, stimulant medication was titrated up to the most effective dose, while minimizing side effects. Therefore our titration procedure might explain that side effects were less present in our study compared to most other studies. A study of Faraone et al.[36] used, similar to our study, a titration protocol to determine the optimal dose of long acting methylphenidate. This study also found no effects on sleep quality after a prolonged period of stimulant medication use.[36] Whereas stimulant medication is known for a negative impact on sleep quality,[35] it has been theorized that neurofeedback would improve sleep quality. The training of sensorimotor-rhythm (SMR) 12-15Hz, as part of theta/beta and theta/SMR training, would enhance sleep spindle density during sleep. Enhanced sleep spindle density has been found to decrease sleep latency and increase total sleep time in a healthy human population.[37] Accordingly, after theta/beta neurofeedback, sleep quality would be expected to improve. However, in line with previous RCTs testing the effects of neurofeedback,[38,39] the current study did not show such positive effects.

The present study is a valuable contribution to the current neurofeedback literature in children with ADHD as it compared neurofeedback, as a stand-alone intervention, with an optimal dose of methylphenidate, the most widely used intervention for ADHD. This study successfully randomly allocated participants to intervention groups, did not suffer from selective drop out, and groups did not differ from each other at pre-intervention. During the neurofeedback sessions, active learning strategies were applied. Nevertheless, there are also some limitations that should be addressed. First, the present study used a theta/beta neurofeedback protocol with the aim to decrease symptoms of ADHD. The selection and application of the training protocol for neurofeedback in ADHD is a prominently debated topic. Recent findings on theta/beta training revealed non-significant results as rated by probably blinded assessors.[12] Up until now, slow cortical potential training, another type of neurofeedback protocol, has not been subjected to intensive research in ADHD and might lead to better results.[40] Second, in contrast to the effects of physical activity found in the current study, a recent study of Hoza et al.[41] revealed that physical activity led to a larger decrease in inattentive behavior in children at risk for developing ADHD and TD children, than a sedentary control condition.[41] This difference in findings might be the result of differences in ADHD-symptom severity, with the current study including children with more severe ADHD-symptoms and a DSM-IV-TR diagnosis of ADHD. Furthermore, the study of Hoza et al. [41] applied a more intensive physical activity protocol than the current study, with three bounds of eight minutes, five times a week for 12 successive weeks. In the current study, the physical activity intervention was implemented as a semi-active control condition, where frequency and intensity

were adjusted to be similar to the neurofeedback intervention. Therefore, a less intensive protocol was applied with 10 bounds of two minutes moderate to vigorous physical activity, three times a week for 10 successive weeks. Accordingly, the physical activity protocol of the current study does not correspond with the recommendations on physical activity found in the literature.[19] More research on physical activity is necessary to substantiate its possible chronic effects on problem behavior as seen in ADHD. Third, in the current study children in the medication condition were prescribed short-acting MPH. However, for some patients the use of long-acting MPH might be preferable over short-acting MPH, considering the increased compliance and reduced social stigma associated with long-acting MPH.[42]

Conclusion

In the present study we found superior behavioral effects of stimulant medication compared to neurofeedback. Furthermore, similar effects were found for neurofeedback and the semi-active control intervention. Neurofeedback is an expensive and time-consuming intervention. Hence, the current study does not support the use of theta/beta neurofeedback training as a stand-alone intervention for children with ADHD.

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Supplementary Appendix 1

Neurofeedback. The THERAPRAX® EEG Biofeedback system (Neuroconn GmbH, Germany) with a DC-amplifier and a sampling rate of 128Hz was used to transmit and analyze the EEG signal. Reference and ground electrodes were attached to right and left mastoids, respectively. Electro-oculogram was obtained with two electrodes at external canthi, and two electrodes at supra- and infraorbital sides. Ocular correction was applied as described in Schlegelmilch et al.(2004). Subsequently, a theta/beta index [theta(μV/Hz)-beta(μV/Hz)/theta(μV/Hz)+beta(μV/Hz) was computed with a short-time-fourier transformed moving average for direct feedback.

Each training session started with a 1-minute baseline theta/beta index measurement, followed by 10 runs of neurofeedback.. Each run comprised four 30-second epochs. The first run of the first training started on a training level with the aim to reduce the theta/beta index with 3%. The training level increased or decreased based on performance of former runs and could range between 3-52%, relative to training session baseline, over the total treatment period of 10 weeks. Number of credits per trial depended on the training level, with more credits for higher levels.

Supplementary Table 1. Complete case analyses of outcome measures and side effects

Questionnaire			Pre-Intervention	Post-Intervention	Adjusted difference	Time			Group x time		
		n	*M(SD)*	*M(SD)*	*M*[95% *CI*]	*F*	η_p^2	*p*	*F*	η_p^2	*p*
Parent ratings											
SDQ	NFB	38	16.76(4.52)	14.74(5.95)	-2.03[-3.40, -0.65]	30.70	0.24	.001	1.44	0.03	.24
	MPH	31	16.03(4.15)	12.81(5.33)	-3.23[-4.76, -1.69]						
	PA	34	17.50(3.69)	15.97(4.55)	-1.53[-2.93, -0.13]						
SWAN-IN	NFB	38	1.44(0.51)	1.12(0.67)	-0.33[-0.54, -0.11]	51.93	0.34	<.001	10.54	0.17	<.001
	MPH	31	1.40(0.73)	0.50(0.82)	-0.90[-1.17, -0.64]						
	PA	34	1.33(0.68)	1.14(0.71)	-0.19[-0.40, 0.23]						
SWAN-H/I	NFB	38	1.30(0.71)	1.01(0.82)	-0.29[-0.52, -0.07]	32.84	0.25	<.001	3.00	0.06	.06
	MPH	31	1.10(0.67)	0.49(0.82)	-0.61[-0.85, -0.36]						
	PA	34	1.21(0.82)	0.98(0.77)	-0.23[-0.45, -0.01]						
Teacher ratings											
SDQ	NFB	37	14.22(4.65)	15.14(5.15)	0.92[-0.49, 2.33]	3.46	0.04	.066	8.03	0.16	.001
	MPH	30	13.73(5.28)	10.23(6.35)	-3.50[-5.31, -1.70]						
	PA	29	15.86(5.46)	15.93(5.12)	0.07[-1.48, 1.62]						
SWAN-IN	NFB	37	1.37(0.91)	1.26(0.76)	-0.11[-0.33, 0.11]	36.09	0.28	<.001	21.79	0.32	<.001
	MPH	30	1.53(0.60)	0.49(0.75)	-1.05[-1.33, -0.77]						
	PA	29	1.31(0.70)	1.25(0.72)	-0.07[-0.28, 0.15]						
SWAN-HI	NFB	37	1.15(0.92)	1.12(1.13)	-0.03[-0.30, 0.25]	10.56	0.10	.002	8.38	0.15	<.001
	MPH	30	0.94(1.30)	0.18(0.92)	-0.76[-1.15, -0.38]						
	PA	29	1.16(0.88)	1.14(0.91)	-0.03[-0.22, 0.16]						
Side effects											
SDSC	NFB	38	45.32(10.55)	43.16(9.45)	-2.16[-4.82, 0.51]	3.24	0.03	.075	0.39	0.01	.68
	MPH	29	45.41(9.22)	44.76(9.61)	-0.66[-3.52, 2.21]						
	PA	32	46.72(13.00)	45.59(11.22)	-1.13[-3.14, 0.89]						

Note. CI=Confidence Interval, H/I=Hyperactivity/Impulsivity scale, IN=Inattention scale; M=Mean, SD=Standard Deviation, SDSC=Sleep Disturbance Scale for Children, SDQ=Strength and Difficulty Questionnaire, SWAN=Strengths and Weaknesses in ADHD and Normal Behaviors; *df* Time: *df*(1,100) Parent ratings, *df*(1,93) Teacher ratings, *df*(1,96) Side effects; *df* Group x Time: *df*(2,100) Parent ratings, *df*(2,93) Teacher ratings, *df*(2,93) Side effects.

Chapter 4

A 6-month follow-up of an RCT on behavioral and neurocognitive effects of neurofeedback in children with ADHD

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Abstract

Objective: To assess the long-term effects of neurofeedback (NFB) in children with attention deficit hyperactivity disorder (ADHD), we compared behavioral and neurocognitive outcomes at a six-month naturalistic follow-up of a randomized controlled trial (RCT) on NFB, methylphenidate (MPH), and physical activity (PA).

Method: Ninety-two children with a DSM-IV-TR ADHD diagnosis, aged 7−13, receiving NFB (n = 33), MPH (n = 28), or PA (n = 31), were re-assessed six-months after the interventions. NFB comprised theta/beta training on the vertex (cortical zero [Cz]). PA comprised moderate to vigorous intensity exercises. Outcome measures included parent and teacher behavioral reports, and neurocognitive measures (auditory oddball, stop-signal, and visual spatial working memory tasks).

Results: At follow-up, longitudinal hierarchical multilevel model analyses revealed no significant group differences for parent reports and neurocognitive measures (p = .058−.997), except for improved inhibition in MPH compared to NFB (p = .040) and faster response speed in NFB compared to PA (p = .012) during the stop-signal task. These effects, however, disappeared after controlling for medication use at follow-up. Interestingly, teacher reports showed less inattention and hyperactivity/impulsivity at follow-up for NFB than PA (p = .004−.010), even after controlling for medication use (p = .013−.036).

Conclusions: Our findings indicate that the superior results previously found for parent reports and neurocognitive outcome measures obtained with MPH compared to NFB and PA post intervention became smaller or non-significant at follow-up. Teacher reports suggested superior effects of NFB over PA; however, some children had different teachers at follow-up. Therefore, this finding should be interpreted with caution.

Introduction

Attention deficit hyperactivity disorder (ADHD) is characterized by symptoms of inattention, as well as hyperactivity and impulsivity,[1] and is often accompanied by impairments in neurocognitive functioning, such as deficits in attention, inhibition, and working memory.[2-5] Stimulant medication is effective and frequently used as a treatment for behavioral[6] and neurocognitive[7] impairments found in ADHD. Despite the benefits, adverse side effects[8] and limited evidence for the long-term effects of stimulant medications[9] have led to the search for alternative treatments for ADHD.

Neurofeedback has been used as a potentially successful non-pharmacological treatment for ADHD.[10,11] This alternative treatment intends to alter brain activity by providing feedback of electroencephalogram (EEG) activity. The majority of studies on neurofeedback have made use of EEG training of theta/beta and/or sensorimotor rhythm (SMR) activity.[12] In this study, we focus on EEG training of theta/beta activity. The rationale for this neurofeedback protocol stems from findings of increased theta (4−7 Hz) and decreased beta activity (13−20 Hz) in children with ADHD compared to typically developing (TD) children.[13] Increased theta activity is related to lower vigilance and decreased beta activity is associated with reduced attention.[14]

The results of randomized controlled trials on the effects of neurofeedback in children with ADHD are mixed.[15,16] In a previous study, we reported on the direct post-intervention effects of neurofeedback compared to stimulant medication and physical activity (semi-active control condition), showing superior effects of stimulant medication compared to neurofeedback and the semi-active control condition in decreasing behavioral symptoms[17] and improving neurocognitive functioning[18] in ADHD. An important remaining issue, however, is whether treatment effects persist[19,20] and/or whether possible delayed effects occur. Findings concerning the long-term effects of neurofeedback, comparing treatment as usual combined with neurofeedback to treatment as usual, are mixed.[21,22] Bink et al.[21] found no additional effect at one-year follow-up of theta/SMR neurofeedback training on either behavioral or neurocognitive outcome measures. Steiner et al.[22] found sustained improvement in children in the theta/beta neurofeedback training group on behavioral outcome measures and executive functioning compared to the treatment as usual group at six-month follow-up. Similar to the findings of Steiner et al.,[22] Gevensleben et al.[23] also found positive effects of theta/beta neurofeedback training on behavioral measures compared to computerized attention skills training at six-month follow-up. There are two RCT studies that compared the long-term effects of neurofeedback to stimulant medication. The study of Meisel et al.[42] found similar behavioral improvement for theta/beta neurofeedback training and

stimulant medication both post intervention and at six-month follow up. In contrast, the study of Moreno-Garcia et al.[24] found better post-intervention attentional functioning assessed by a neurocognitive task in those treated with stimulant medication compared to those treated with theta/beta neurofeedback, but group differences disappeared at two-month follow-up.

In sum, neurofeedback is a potentially effective treatment for behavioral and neurocognitive symptoms in ADHD. However, the results for both short-term and long-term effects of neurofeedback are mixed. Furthermore, studies on long-term effects are limited in number and vary in terms of control conditions. Therefore, in this RCT, we compared the behavioral and neurocognitive effects of neurofeedback to stimulant medication, and to a semi-active control condition consisting of a physical activity intervention to control for non-specific treatment effects at six-month naturalistic follow-up. Behavioral effects were evaluated by both parents and teachers. Neurocognitive functioning was assessed using measures of attention, inhibition, and visual spatial working memory. In addition, secondary measures evaluated possible side effects using quality of sleep.

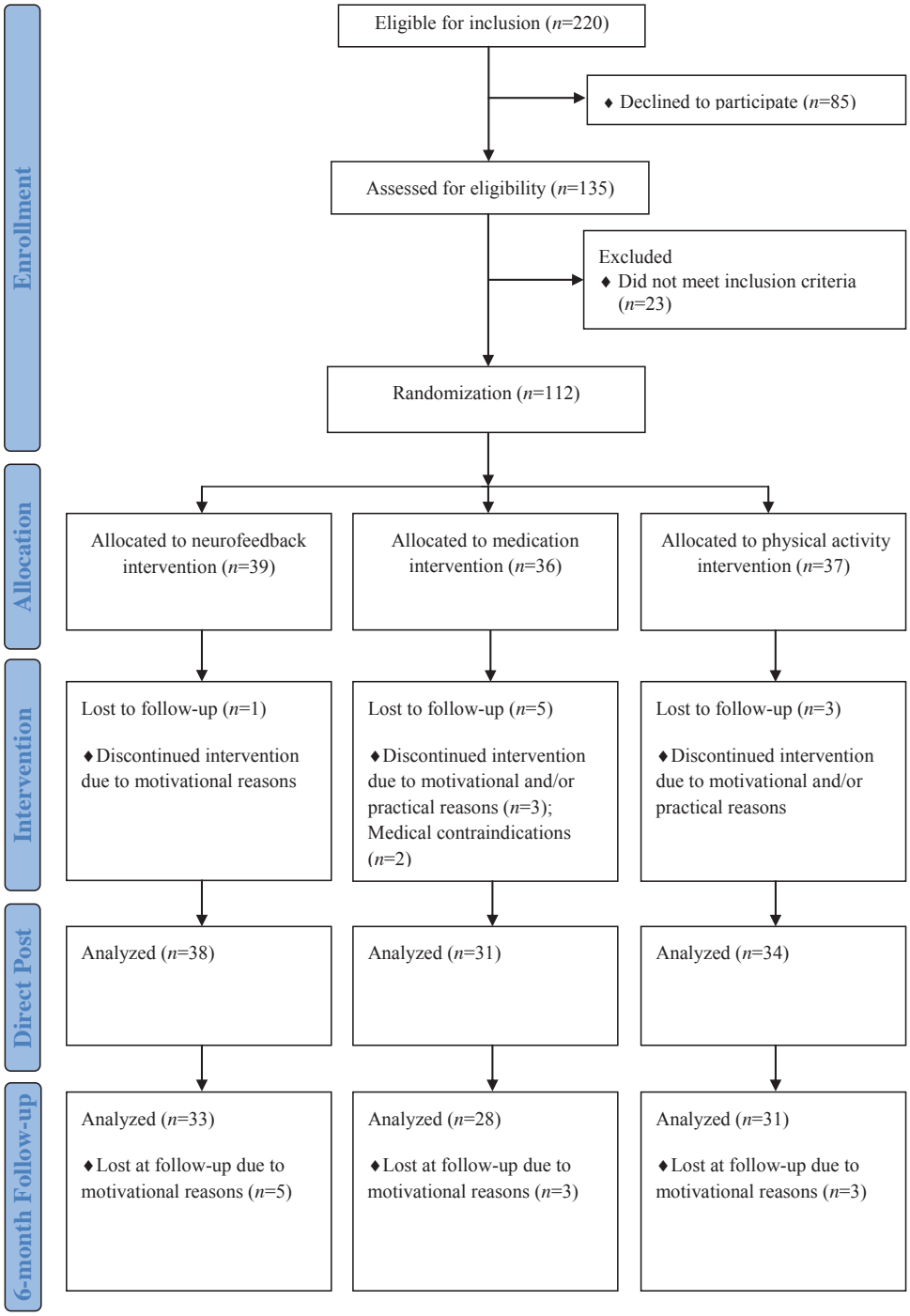
Methods

Participants

Eligible participants were Dutch-speaking children, aged 7-13 years old, with a primary clinical diagnosis of ADHD established using DSM-IV-TR criteria.[1] Children with ADHD were recruited from 15 child mental health outpatient care facilities in the west of the Netherlands. Before entering the study, parent and teacher ratings on the Disruptive Behavior Disorders Rating Scale (DBDRS)[25] confirmed the children's diagnosis; at least one of the scores on the Inattention or Hyperactivity/Impulsivity scales had to be above the 90th percentile for one of the informants, and above the 70th percentile for the other informant (signifying pervasiveness of symptoms). At study entry, all children had been free of stimulant use for at least one month. Exclusion criteria were neurological disorders and IQ below 80 as measured by a four subtest version of the Wechsler Intelligence Scale of Children-III (WISC-III), including the subtests Vocabulary, Arithmetic, Block Design, and Picture Arrangement.[26] No restrictions were set on other comorbidities. Comorbid disorders were diagnosed according to DSM-IV-TR and retrieved from the clinical records. Comorbid disorders included learning disorders (NFB $n = 5$, MPH $n = 2$, PA $n = 1$), autism spectrum disorders (NFB $n = 3$, MPH $n = 2$, PA $n = 3$), anxiety disorders (NFB $n = 2$, MPH $n = 0$, PA $n = 2$), and mood disorder (NFB $n = 1$, MPH $n = 0$, PA $n = 0$). Chi square testing revealed no significant differences in the distribution of comorbid disorders over groups (χ^2 (8, $n = 112$) = 12.88, $p = .12$).

Initially, 112 children with ADHD were randomized to one of the three intervention groups: NFB (n = 39), MPH (n = 36), or PA (n = 37). At six-month follow-up, a total of 20 children had dropped out of the study. The numbers of children who dropped out were similarly distributed across the three intervention groups (NFB n = 6 [15.4%], MPH n = 8 [22.2%], PA n = 6 [16.2%], p = .705, two-tailed Fisher's exact test). In total, 92 children participated in the six-month follow-up measurement, NFB (n = 33), MPH (n = 28), and PA (n = 31). Figure 1 presents a flow diagram of participants.

Figure 1. Flow diagram of participants



Trial design

A multicenter three-way parallel group study with balanced randomization was conducted. A randomization table was created using a computerized random number generator.[27] Stocks of nine unmarked sealed envelopes were presented to parents at intake. Parents randomly picked an envelope revealing the intervention allocation. Subsequently, children, parents, and teachers were aware of the allocated group. The trial was registered on clinicaltrials.gov (Ref. No. NCT01363544).

Interventions

The NFB and PA treatments consisted of 30 individual training sessions that were offered three times a week over a period of 10-12 weeks. Each session lasted 45 min, including 20 min of effective training. All interventions, as described below, took place after the pre-intervention assessment. A full description of the interventions can be found in previous reports.[17,18]

Neurofeedback. Theta/beta training was applied with the aim of inhibiting theta activity (4−8 Hz) and reinforcing beta activity (13−20 Hz) at the vertex (cortical zero [Cz]). The theta/beta index was represented to the participant by simple graphics on a screen. Successful reduction of the theta/beta index as averaged over one trial relative to the session baseline was rewarded with the appearance of a sun and granted credits. To promote generalization of the strategies learned to daily life, transfer trials were used. The mean number of training sessions for participants (n = 38) who completed the assessments post intervention was 29 (M = 28.53, SD = 2.63, range 19−30). The mean number of training sessions for participants (n = 33) who completed the assessments at follow-up was 29 (M = 28.94, SD = 1.75, range 22−30).

Medication. After the pre-intervention assessment, a four-week double-blind randomized placebo-controlled titration procedure was used to determine the optimal individual dose of short-acting methylphenidate (MPH).[28] In total, 31 children completed the titration procedure. Children were classified by a standardized procedure[29] as responders when their ADHD symptoms decreased significantly compared to placebo (n = 29). The two non-responders were treated with 5 mg MPH twice daily. The child's psychiatrist prescribed the optimal dose for the remaining intervention period (5 mg for 10 children, including 8 responders and 2 non-responders; 10 mg for 14 children; 15 mg for 2 children; 20 mg for 5 children). At follow-up, 21 children were using medication, while 6 children discontinued medication usage.

Physical activity. Each training session started with 5 min of warm up, followed by five 2-min moderate intensity exercises at a level of 70−80% of maximum heart rate (HRmax). After

a 5-min break, five 2-min vigorous intensity exercises at 80−100% of HRmax were performed. Time and heart rate were monitored and registered using a POLAR FT4 watch (Polar Electro Oy, Kempele, Finland). The mean number of sessions for participants who completed the assessments post intervention (n = 34) was 28 (M = 27.74, SD = 3.56, range 12−30). The mean number of training sessions for participants who completed the assessments at follow-up (n = 31) was 28 (M = 28.29, SD = 2.30, range 19−30).

Outcome measures

A full description of the outcome measures can be found in previous papers.[17,18] The following behavioral and neurocognitive measures were used to assess long-term outcomes.

Behavioral outcome measures. Scores on the parent- and teacher-reported Strength and Difficulty Questionnaire (SDQ)[30,31] and Strengths and Weaknesses of ADHD symptoms and Normal Behavior Scale (SWAN)[32] were used as primary outcome measures. The Total scale of the SDQ (assessing behavioral problems) and the SWAN Inattention and Hyperactivity/Impulsivity scales served as dependent measures.

Neurocognitive outcome measures. The auditory oddball task was used to measure attention.[33] Outcome measures were response speed (mean reaction time; MRT), assessing attention, and the coefficient of variation (CV) [CV = MRT SD/MRT], a measure of attentional lapses. Omission and commission errors were uncommon, and therefore excluded from analyses. The stop-signal task (SST) was primarily used to measure inhibition.34 Variables of interest were: (1) stop-signal reaction time (SSRT), a measure of the speed of the inhibitory process, calculated by subtracting the mean stop-signal delay (SSD) from MRT; (2) number of commission errors in stop trials, measuring impulsivity; (3) number of omission errors in go trials, assessing attention; (4) response speed (MRT), and (5) variability of response speed calculated by the coefficient of variation (CV), measuring lapses of attention. The visual spatial working memory task (VSWM)35,36 was used to assess short-term storage or maintenance of visuospatial information (forward condition) and visuospatial working memory (backward condition). Variables of interest were the number of correct trials taken from the two conditions.

Secondary outcome measures. Secondary measures included the Sleep Disturbance Scale (SDSC), used to assess the quality of sleep as reported by parents.[37] The total score was used as the dependent measure.

Procedure

The study was approved by the national medical ethics committee (NL 31641.029.10 CCMO). Written informed consent was obtained before participation from all parents and children aged 11 years and older.

Pre-intervention assessment took place in the week prior to the start of the intervention. Post-intervention assessment took place one week after the last training. At follow-up, six months later, the assessment included measurements identical to those used in prior assessments. Post-intervention effects have been reported previously.[17,18,38-40] During post-intervention assessment, the MPH group continued use of medication. Interventions took place between September 2010 and March 2014. The six-month follow-up was naturalistic and children were allowed to start, continue, or stop interventions, including the use of stimulant medication.

Statistical methods

Statistical analyses were performed in IBM SPSS Statistics, version 20.0.[41] Differences between intervention groups in terms of background characteristics were analyzed using a chi square (χ^2) test or one-way analysis of variance (ANOVA) with Tukey post-hoc analyses for group comparison.

Attrition analyses were performed with ANOVAs on sample characteristics and pre-intervention outcome measures comparing the initially randomized sample to the sample that completed the assessment at follow-up. At post-intervention assessment, teacher reports on the SDQ and the SWAN were missing for 2 participants, and the SDSC was missing for 10 participants. At follow-up, parent reports on the SDQ and the SWAN were missing for 2 participants, and teacher reports on the SDQ and the SWAN were missing for 3 participants. SDSC data were missing for 6 participants. At post-intervention assessment, data for 23 participants on the oddball task and 10 participants on the stop-signal task were not available for analysis due to technical problems or misinterpretation of the task, respectively. At follow-up, data for 19 participants on the oddball task and 4 participants on the stop-signal task were not available for analysis.

Post-intervention effects have been reported previously.[17,18] This study evaluated long-term effects, analyzed with linear mixed models. Mixed models were used because the outcomes post intervention and at follow-up were clustered within subjects. The between-subject factor "group," the within-subject factor "time" (post intervention and follow-up), and the interaction "group x time" were added in the model while adjusting for possible pre-intervention group differences on the dependent measures. NFB was used as a reference group to compare intervention effects with those obtained using stimulant medication (MPH versus NFB) and physical activity

(PA versus NFB). For all group comparisons, we report the difference scores, beta scores, and the 95% confidence interval [95%CI]. Results were regarded significant at $p \leq .05$.

Because children were allowed to start, continue, or stop stimulant medication use during the follow-up interval (post intervention to follow-up), we also performed sensitivity analyses. These sensitivity analyses included only those children in the NFB and PA intervention groups who were not using medication at follow-up, and children in the MPH intervention who continued the use of stimulant medication at follow-up.

Results

Group characteristics

Group characteristics are displayed in Table 1. Group characteristics did not differ between treatment groups for the participants who completed the study at six-month follow-up, except for medication use at follow-up ($p < .05$). Post-hoc tests showed less stimulant medication use at follow-up in the NFB and PA groups compared to the MPH group. Medication use at follow-up did not differ between the NFB and PA group. In addition, behavioral and neurocognitive outcome measures did not differ between treatment groups for participants who completed the study at six-month follow-up.

Table 1. Group characteristics

	NFB (*n*=33)		MPH (*n*=28)		PA (*n*=31)		Group	
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
Age (years)	9.81	1.86	8.97	1.22	9.55	1.76	1.98	ns
IQ	100.88	13.84	102.14	14.90	98.94	12.91	0.40	ns
Gender, (M/F)	24/9		22/6		24/7		0.33[a]	ns
Stimulant medication at T2 (On/Off)	12/20		21/7		14/17		8.70	.01
Parent rating								
DBDRS								
Inattention	16.58	5.12	16.00	5.71	16.00	5.00	0.13	ns
H/I	13.73	5.84	12.50	5.75	12.97	6.24	0.33	ns
Teacher rating								
DBDRS								
Inattention	15.76	5.27	17.00	6.44	15.26	5.68	0.70	ns
H/I	13.90	7.00	12.11	9.64	12.32	7.42	0.46	ns

Note. DBDRS=Disruptive Behavior Disorder rating scale; H/I=Hyperactivity/Impulsivity scale; M=Mean; SD=Standard Deviation; y=years; [a]$\chi(2)$.

Attrition analysis

There were no differences in sample characteristics and pre-treatment behavioral and neurocognitive outcome measures between the initially randomized sample and the sample that completed follow-up assessment.

Behavioral outcome measures

Behavioral results are presented in Table 2. Sensitivity analyses, considering medication use at follow-up, are presented in Supplementary Table 1.

Parent reports. For the parent-reported SDQ Total scale score, no significant group x time effects were found and no significant group differences were found at follow-up. On the SWAN Inattention scale, parent-reported inattention showed a significant group x time interaction for the MPH and NFB group contrast ($p = .002$). Post intervention, children in the MPH group showed fewer inattention symptoms compared to the NFB group ($p < .001$). However, this difference disappeared at follow-up. For the PA versus NFB group contrast, we found no significant group x time effect, nor did the two groups differ at follow-up. For parent-reported values on the SWAN Hyperactivity/Impulsivity scale, the group x time interaction was significant for the MPH and NFB group contrast ($p = .002$). Post intervention, children in the MPH group showed fewer symptoms of hyperactivity/impulsivity than those who had received NFB ($p = .014$). However, this difference disappeared at follow-up. For the PA and NFB group contrast, the group x time interaction was not significant and groups did not differ at follow-up.

When the analyses were rerun comparing only those children in the NFB and PA groups who were not using medication at follow-up, and children in the MPH group who continued stimulant medication use at follow-up, the results remained unchanged. In sum, the results of parent reports showed that from post intervention to follow-up, children initially randomized to NFB caught up with children who participated in the MPH group. There were no differences over time between children who received NFB and PA.

Teacher reports. Teacher reports on the SDQ Total scale score showed a significant group x time interaction for the MPH and NFB group contrast ($p = .038$). Post intervention, children in the MPH group showed fewer behavioral problems compared to the NFB group ($p < .001$). This difference disappeared at follow-up. For the PA versus NFB group contrast, a significant group x time interaction was also found ($p = .033$). Post intervention, the two groups did not differ; however, at follow-up, children in the NFB group showed fewer behavioral problems compared to children in the PA group ($p = .010$).

On the SWAN Inattention scale, teacher-reported inattention showed a significant group x time interaction for the MPH versus NFB group contrast (p = .010). Post intervention, children in the MPH group showed fewer inattention symptoms compared to the NFB group (p < .001); however, this difference disappeared at follow-up. For the PA and NFB group contrast, a significant interaction was also found (p = .024). Post intervention, the PA and NFB groups did not differ; however, at follow-up, children in the NFB group showed fewer inattention symptoms than the PA group (p = .006).

For the Hyperactivity/Impulsivity scale, teacher-reported hyperactivity/impulsivity showed a significant group x time interaction for the MPH versus NFB group contrast (p = .005). Post intervention, children in the MPH group showed fewer hyperactivity/impulsivity symptoms compared to the NFB group (p < .001). This difference disappeared at follow-up. For the PA and NFB group contrast, the group x time interaction was also significant (p=.013). At post-intervention assessment, no difference was found between NFB and PA; however, at follow-up, children in the NFB group showed fewer hyperactivity/impulsivity symptoms compared to the PA group (p = .004).

The results of sensitivity analyses for the SDQ were similar to the main analyses for the MPH versus NFB group contrast. Only for the PA versus NFB group contrast, did the time x group interaction (p = .033) turn non-significant (p = .205). The results of sensitivity analyses for the SWAN scales were similar to our main analyses, except for the significant group x time interaction in hyperactivity/impulsivity symptoms for the PA versus NFB group contrast (p = .013), which became non-significant when excluding stimulant-using children in the PA and NFB groups, and non-stimulant users in the MPH group (p = .110).

In sum, the results of the teacher reports showed that from post intervention to follow-up, children who received NFB caught up with children in the MPH group. Analyses of the teacher reports for children in the NFB group and the PA group showed that at follow-up children in the NFB group had improved to a greater extent compared to those in the PA group. Sensitivity analyses showed similar results at follow-up compared to the main analyses. However, two of the three significant group x time interactions between NFB and PA disappeared.

Neurocognitive outcome measures.

The neurocognitive results are presented in Table 2. Sensitivity analyses are presented in Supplement 1.

Oddball task. For both MRT and CV, no significant group x time effects and no significant group differences were found at follow-up, indicating groups did not differ on attentional functioning. Due to technical problems or misinterpretation of the oddball task, the groups became too small to perform sensitivity analyses.

Stop-signal task. For SSRT, the group x time interaction was significant for the MPH versus NFB group contrast ($p = .018$). Post intervention, children in the MPH group showed faster inhibitory control processes compared to children in the NFB group ($p < .001$), and although differences became smaller, differences between the two groups remained significant at follow-up ($p = .040$). For the PA versus NFB group contrast, the group x time interaction was not significant and the two groups did not differ at follow-up.

For commission and omission errors, no significant group x time effects were found and no significant group differences were found at follow-up, indicating groups did not differ on impulsivity and attention, respectively.

In terms of MRT, no significant group x time effects and no significant group differences were found at follow-up for the MPH and NFB group contrast. For the PA versus NFB group contrast, no significant group x time interaction was found. Post intervention the two groups did not differ; however, at follow-up, children in the NFB group showed a faster MRT compared to those in the PA group ($p = .012$). For CV, response speed variability, no significant group x time effects were found and no significant group differences were found at follow-up.

The results of sensitivity analyses for the stop-signal task were similar to those of our main analyses, except for measures of SSRT, omission errors, and MRT. For SSRT, the MPH and NFB group contrast revealed a non-significant group x time interaction ($p = .188$), and group differences at follow-up also disappeared ($p = .098$). For omission errors, the MPH and NFB group contrast became significant for group differences at follow-up, showing fewer omission errors for children in the MPH group compared to the NFB group at follow-up ($p = .046$). The PA and NFB group difference for MRT at follow-up turned non-significant ($p = .221$).

Visual spatial working memory (VSWM) task. The results of the VSWM for the forward and backward condition showed no significant group x time effects and no significant group differences at follow-up, indicating no difference between groups for short-term storage and working memory. The results of the sensitivity analyses for the VSWM task for both conditions were similar to those obtained in the main analyses.

In sum, the neurocognitive measures showed no differences between children in the MPH and NFB groups at follow-up, except for faster inhibitory control processes in the MPH group

measured by SSRT in the stop-signal task. However, this effect disappeared in the sensitivity analyses. The PA and NFB group contrasts showed no group differences at follow-up on the neurocognitive measures, except for faster MRTs measured with the stop-signal task in the NFB group. However, this finding was not substantiated in the sensitivity analyses. Taken together, no differences were found at follow-up on any of the neurocognitive measures between the MPH and NFB groups or between the PA and NFB groups.

Secondary outcome measures

On the SDSC Total scale we found no significant effects for quality of sleep as reported by parents. The results of the sensitivity analyses were similar to those of the main analyses.

Table 2. Results of mixed models analyses evaluating long-term effects of neurofeedback

		Pre-intervention		Post-intervention		Follow-up		Comparison groups	Difference score post-intervention			Difference score follow-up			Group x Time
		n	*M*(*SD*)	*n*	*M*(*SD*)	*n*	*M*(*SD*)		beta	95% *CI*	*p*	beta	95% *CI*	*p*	*p*
Behavioral outcome measures															
Parent ratings															
SDQ	NFB	39	16.90(4.54)	38	14.74(5.95)	32	13.34(5.87)	MPH vs NFB	-1.40	(-3.43, 0.64)	.177	0.03	(-2.14, 2.20)	.977	.279
	MPH	36	15.64(4.23)	31	12.81(5.33)	28	12.50(4.41)	PA vs NFB	0.70	(-1.29, 2.68)	.490	1.55	(-0.58, 3.68)	.152	.507
	PA	37	17.22(3.93)	34	15.97(4.55)	30	15.30(4.46)								
SWAN-IN	NFB	39	1.42(0.52)	38	1.12(0.67)	32	0.81(0.72)	MPH vs NFB	-0.60	(-0.90, -0.29)	<.001	-0.06	(-0.38, 0.26)	.720	.002
	MPH	36	1.39(0.70)	31	0.49(0.82)	28	0.60(0.62)	PA vs NFB	0.09	(-0.21, 0.39)	.561	0.29	(-0.02, 0.61)	.068	.211
	PA	37	1.28(0.70)	34	1.14(0.71)	31	1.02(0.82)								
SWAN-H/I	NFB	39	1.30(0.70)	38	1.01(0.82)	32	0.60(0.71)	MPH vs NFB	-0.38	(-0.68, -0.08)	.014	0.09	(-0.22, 0.41)	.551	.002
	MPH	36	1.14(0.72)	31	0.49(0.82)	28	0.55(0.71)	PA vs NFB	0.03	(-0.26, 0.32)	.823	0.22	(-0.09, 0.52)	.162	.198
	PA	37	1.28(0.82)	34	0.98(0.77)	31	0.83(0.92)								
Teacher ratings															
SDQ	NFB	39	14.51(4.71)	37	15.14(5.15)	33	11.24(5.15)	MPH vs NFB	-4.64	(-7.10, -2.19)	<.001	-1.21	(-3.80, 1.40)	.355	.038
	MPH	33	13.48(5.43)	30	10.23(6.35)	27	9.52(6.10)	PA vs NFB	-0.11	(-2.60, 2.37)	.929	3.41	(0.84, 6.00)	.010	.033
	PA	35	15.91(5.17)	29	15.93(5.12)	29	15.83(6.63)								
SWAN-IN	NFB	39	1.40(0.90)	37	1.26(0.76)	33	0.59(1.00)	MPH vs NFB	-0.86	(-1.22, -0.51)	<.001	-0.28	(-0.65, 0.10)	.148	.010
	MPH	33	1.52(0.62)	30	0.49(0.75)	27	0.39(0.97)	PA vs NFB	0.01	(-0.35, 0.37)	.956	0.52	(0.15, 0.90)	.006	.024
	PA	35	1.38(0.69)	29	1.25(0.72)	29	1.08(0.74)								
SWAN-H/I	NFB	39	1.18(0.92)	37	1.12(1.13)	33	0.40(0.96)	MPH vs NFB	-0.83	(-1.21, -0.45)	<.001	-0.18	(-0.60, 0.21)	.366	.005
	MPH	33	0.93(1.25)	30	0.18(0.92)	27	0.04(0.80)	PA vs NFB	0.01	(-0.40, 0.40)	.961	0.60	(0.20, 0.98)	.004	.013
	PA	35	1.12(0.92)	29	1.14(0.91)	29	0.98(0.89)								
Neurocognitive otcome measures															
Oddball task															
MRT	NFB	32	442.88(97.05)	31	438.27(93.60)	25	420.51(88.18)	MPH vs NFB	-56.44	(-85.00, -28.00)	<.001	-29.00	(-61.15, 3.17)	.077	.081
	MPH	30	464.31(69.12)	28	398.19(60.46)	21	417.40(79.38)	PA vs NFB	13.63	(-13.90, 41.12)	.328	17.30	(-11.67, 46.25)	.240	.793
	PA	33	441.08(89.34)	28	440.85(90.12)	27	424.13(88.40)								
CV	NFB	32	0.30(0.08)	31	0.28(0.07)	25	0.28(0.08)	MPH vs NFB	-0.02	(-0.05, 0.01)	.139	-0.04	(-0.07,<0.01)	.058	.573
	MPH	30	0.28(0.04)	28	0.28(0.12)	21	0.24(0.04)	PA vs NFB	<-0.01	(-0.03, 0.03)	.866	<-0.01	(-0.04, 0.03)	.851	.979
	PA	33	0.29(0.06)	28	0.28(0.07)	27	0.27(0.05)								

Stop-signal task														
SSRT	NFB	37	270.61(75.06)	35	254.36(84.34)	30	216.05(69.17)	MPH vs NFB	-74.73	(-106.56, -42.91)	<.001	-35.28	(-68.88, -1.68)	.040	.018
	MPH	33	278.08(91.36)	28	182.32(75.41)	24	188.04(87.66)	PA vs NFB	-2.52	(-33.64, 28.60)	.873	-0.11	(-31.80, 31.59)	.995	.878
	PA	37	257.61(89.40)	30	237.81(87.39)	31	214.07(83.58)								
Commission	NFB	37	20.08(13.83)	35	18.51(15.11)	30	15.53(11.37)	MPH vs NFB	-6.58	(-11.81, -1.34)	.014	-4.20	(-9.78, 1.38)	.139	.433
	MPH	33	19.67(11.35)	28	11.93(9.43)	24	12.46(15.50)	PA vs NFB	2.68	(- 2.45, 7.80)	.304	3.60	(-1.64, 8.84)	.176	.749
	PA	37	18.43(10.26)	30	19.47(12.40)	31	19.00(15.38)								
Omission	NFB	37	15.57(13.74)	35	13.97(14.28)	30	10.17(10.22)	MPH vs NFB	-7.21	(-12.37, -2.05)	.006	-2.86	(-8.42, 2.69)	.311	.223
	MPH	33	14.18(11.05)	28	5.43(7.34)	24	6.67(9.90)	PA vs NFB	4.36	(-0.72, 9,45)	.092	3.81	(-1.39, 9.01)	.150	.872
	PA	37	14.95(11.74)	30	16.03(15.16)	31	13.20(13.75)								
MRT	NFB	37	635.11(130.39)	35	613.91(122.00)	30	550.36(113.91)	MPH vs NFB	-15.20	(-61.28, 30.88)	.515	27.37	(-21.54, 76.30)	.271	.104
	MPH	33	679.78(122.31)	28	625.26(132.21)	24	598.82(125.40)	PA vs NFB	13.56	(-31.10, 58.23)	.549	58.94	(13.26, 104.61)	.012	.071
	PA	37	636.85(109.25)	30	610.16(122.10)	31	605.32(115.74)								
CV	NFB	37	0.28(0.04)	35	0.27(0.05)	30	0.27(0.05)	MPH vs NFB	-0.01	(-0.03, 0.01)	.348	-0.01	(-0.03, 0.01)	.374	.998
	MPH	33	0.27(0.03)	28	0.25(0.05)	24	0.26(0.05)	PA vs NFB	0.01	(-0.01, 0.03)	.464	<0.01	(-0.01, 0.03)	.437	.952
	PA	37	0.28(0.4)	30	0.27(0.03)	31	0.28(0.04)								
VSWM															
Forward	NFB	39	12.26(2.92)	38	12.74(3.58)	33	13.70(2.94)	MPH vs NFB	0.63	(-0.53,1.78)	.284	0.78	(-0.42, 2.00)	.201	.797
	MPH	36	10.97(2.58)	31	12.39(2.75)	28	13.71(3.07)	PA vs NFB	-0.21	(-1.34,0.92)	.716	-0.50	(-1.67, 0.68)	.404	.621
	PA	37	11.16(2.73)	34	11.53(3.61)	31	12.55(2.64)								
Backward	NFB	39	10.90(3.08)	38	11.68(3.44)	33	11.42(3.62)	MPH vs NFB	1.06	(-0.18, 2,30)	.093	0.93	(-0.36, 2.22)	.158	.843
	MPH	36	9.58(2.45)	31	11.71(3.66)	28	11.82(3.53)	PA vs NFB	0.17	(-1.04, 1.38)	.784	0.43	(-0.83, 1.70)	.497	.687
	PA	37	9.95(2.95)	34	10.76(3.32)	31	11.26(3.56)								
Side effects															
SDSC	NFB	38	45.32(10.55)	39	42.82(9.56)	32	42.81(8.64)	MPH vs NFB	1.41	(-1.84, 4.65)	.393	-0.70	(-4.15, 2.74)	.687	.247
	MPH	35	45.09(9.11)	30	43.93(10.47)	26	42.00(7.83)	PA vs NFB	1.51	(-1.65, 4.70)	.348	1.34	(-2.10, 4.77)	.442	.926
	PA	35	45.97(12.70)	33	45.85(11.14)	28	45.96(11.50)								

Note: Neurofeedback was used as a reference group to compare intervention effects with stimulant medication (MPH versus NFB) and physical activity (PA versus NFB). CI=Confidence Interval, M=Mean; SD=Standard Deviation; SDQ=Strength and Difficulty Questionnaire; SWAN=Strengths and Weaknesses in ADHD and Normal Behaviors; H/I=Hyperactivity/Impulsivity scale; MRT=mean reaction time; CV=coefficient of variation; SSRT=stop-signal reaction time; VSWM=visual spatial working memory; SDSC=Sleep Disturbance Scale for Children.

Discussion

In this study, we analyzed the long-term behavioral and neurocognitive effects of neurofeedback compared to stimulant medication and physical activity in children diagnosed with ADHD. Physical activity was used as a semi-active control condition to control for non-specific effects. Our findings indicate that the superior results previously found in parent reports and neurocognitive outcome measures obtained with stimulant medication post intervention,[17,18] became smaller or non-significant at follow-up. Interestingly, at follow-up, teacher reports showed larger improvements for neurofeedback than for the semi-active control condition. These results might suggest that neurofeedback can have delayed beneficial effects. To rule out confounding effects of medication use during the six-month follow-up, sensitivity analyses were performed only including those subjects assigned to the neurofeedback and semi-active control groups who refrained from the use of stimulant medication to follow-up, and those subjects assigned to the methylphenidate group who continued use of stimulant medication to follow-up. These analyses confirmed our findings obtained in the full sample, with teacher reports showing better results at follow-up for neurofeedback than for the semi-active control condition. However, the results of teacher reports should be interpreted with caution as some children had different teachers at follow-up.

Parent reports and neurocognitive measures showed comparable long-term effects for children who received neurofeedback and for those who were receiving stimulant medication at follow-up, except for the measure of inhibitory control. Similar to the results post intervention, children with stimulant medication showed improved inhibitory control compared to the neurofeedback group at follow-up. However, in line with our other outcome measures, the difference between the two treatment groups became smaller at follow-up compared to post intervention. After controlling for medication use, the difference between the two groups disappeared at follow-up.

Furthermore, our results are in accordance with some but not all previous studies. The RCT study of Meisel et al.[42] also found neurofeedback to be as effective as stimulant medication at follow-up. However, in that study, post-intervention effects revealed no significant differences between neurofeedback and stimulant medication,[42] while our study revealed superior post-intervention effects of medication assessed with parent reports[17] and neurocognitive outcome measures.[18] The results of our study are in line with those of the RCT conducted by Moreno-Garcia et al,[24] who compared the effects of neurofeedback, standard pharmacological treatment, and behavioral therapy. Their study applied the Integrated Visual and Auditory Continuous Performance Test to determine therapeutic effects on attention and response control variables

at pre- and post-testing, and follow-up. Post intervention, treatment with medication showed superior effects compared to treatment with neurofeedback on measures of attention. However, comparable to our findings, their treatment differences were not maintained at follow-up. In this study, we speculate that the effects of stimulant medication remained more or less stable over time, while the neurofeedback and the semi-active control groups revealed similar improvements over time on both parent reports and the neurocognitive outcome measures, except for response speed. However, the superior effect of neurofeedback compared to the semi-active control group on response speed at follow-up disappeared after controlling for medication use. Furthermore, considering that we aimed to control for non-specific effects with the semi-active control group, these improvements over time probably reflect non-specific effects, such as developmental effects and/or regression to the mean, unrelated to specific treatment components.

In contrast to our results for parent reports, Gevensleben et al.[23] found favorable results for neurofeedback at six-month follow-up compared to computerized attention skill training used as a semi-active control intervention. In their study, however, analyses were limited to children who were not taking medication at follow-up, potentially influenced by selection bias. In this study, to avoid such selection bias, we included all children regardless of medication use at follow-up. Moreover, we performed sensitivity analyses comparing non-users in the neurofeedback and semi-active control groups to children in the medication group who continued the use of medication at follow-up. Overall, comparable results were obtained for this sub-group.

Unlike parent reports, teacher reports provided possible evidence of the specificity of improvements for the neurofeedback group compared to the semi-active control group. Our findings may be interpreted as demonstrating the delayed effects of neurofeedback. Arns and Kenemans[43] presented a model in which neurofeedback altered both sleep and ADHD problems in a sub-group of ADHD. They suggested that neurofeedback affects the sleep spindle circuitry, resulting in increased sleep spindle density and normalization of sleep onset insomnia (SOI), thereby affecting the noradrenergic locus coeruleus (LC). This cascade would result in vigilance stabilization and delayed improvements in ADHD symptoms. However, in this study no evidence was found for this hypothesis as we demonstrated comparable improvements in sleep quality for all interventions. According to other predictions of the model, delayed effects of neurofeedback should also be expressed in reduced frontal theta and alpha power. Further research should focus on verifying these predictions by analyzing EEG power spectra at follow-up.

Previous results of studies using teacher reports to assess long-term effects of neurofeedback showed evidence for the effectiveness of a multimodal, combined medication and

neurofeedback intervention in children with ADHD.[44,45] The study of Duric et al.[44] compared the efficacy of three interventions in children with ADHD: medication only, neurofeedback only, and medication and neurofeedback combined (multimodal). None of the three interventions resulted in changes in hyperactivity reported by teachers throughout the entire study. At follow-up, comparable improvements in symptoms of inattention were found for the multimodal and the medication only interventions. In addition, while Duric et al.[44] found neurofeedback to be as effective as medication post intervention, teacher reports at follow-up seemed to indicate an increase in inattention symptoms for the neurofeedback only intervention. These results are in contrast to our results on teacher ratings, which indicated superior effects of methylphenidate compared to neurofeedback post intervention, while similar effects were found for neurofeedback and methylphenidate at follow-up. However, it should be noted that in our study some children had different teachers at follow-up. For this reason, Gevensleben et al.[23] and Steiner et al.[22] excluded teacher reports at follow-up. We reasoned that due to the randomized nature of the trial, the results were not likely to be confounded. However, this made overall teacher reports less reliable and therefore the results should be interpreted with caution.

Some strengths and limitations of the current study should be mentioned. The strengths of this study were the low attrition rates, no baseline group differences at pre-intervention, and the inclusion of both an active control group to account for non-specific changes and a medication control group to assess whether neurofeedback may be a viable alternative for stimulant treatment.

Inevitably, the study comes with some limitations. First, we performed a naturalistic, not experimentally controlled follow-up. Therefore, it is difficult to determine whether the interventions improved long-term functioning at follow-up or potentially unknown factors may have influenced our results. However, controlling for medication use with sensitivity analyses did not fundamentally alter the results. Second, in this study we enrolled 112 participants of the 186 planned. Although the final sample size was more than sufficient to detect medium effect size differences between groups, larger groups would have allowed more statistical power for exploratory analyses. Third, in recent years, the rationale for the theta/beta ratio as a clinical biomarker of ADHD has been questioned.[46-48] Moreover, several research groups have speculated that neurofeedback does not focus on adjusting the neural dysfunction, but rather on learning compensatory mechanisms,[10,49] which may also involve central nervous system (CNS)-specific effects. Fourth, the statistical power of sensitivity analyses was reduced because of the smaller sample size.

In conclusion, our naturalistic long-term follow-up shows that previously established superior post-intervention effects on parent reports and neurocognitive outcome measures of stimulant medication compared to neurofeedback[17,18] become smaller or disappear at follow-up. Only teacher reports show superior effects for the neurofeedback group compared to the semi-active control group at follow-up. However, these results must be interpreted with caution as some children had different teachers at follow-up.

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Supplementary Table 1. Results sensitivity analyses

		Pre-intervention		Post-intervention		Follow-up		Comparison groups	Difference score post-intervention			Difference score follow-up			Group * Time
		n	*M*(*SD*)	*n*	*M*(*SD*)	*n*	*M*(*SD*)		beta	95% *CI*	*p*	beta	95% *CI*	*p*	*p*
Behavioral outcome measures															
Parent ratings															
SDQ	NFB	20	15.65(4.79)	20	14.20(6.27)	20	12.90(6.00)	MPH vs NFB	-2.21	(-4.89, 0.46)	.104	-0.77	(-3.44, 1.91)	.570	.381
	MPH	21	15.67(3.44)	21	12.00(4.95)	21	12.14(3.72)	PA vs NFB	0.69	(-2.20, 3.57)	.638	0.60	(-2.32, 3.52)	.682	.963
	PA	17	18.18(3.84)	17	16.59(4.05)	16	15.06(4.96)								
SWAN-IN	NFB	20	1.42(0.44)	20	1.04(0.80)	20	0.71(0.68)	MPH vs NFB	-0.67	(-1.10, -0.26)	.002	-0.09	(-0.50, 0.32)	.668	.007
	MPH	21	1.34(0.71)	21	0.32(0.77)	21	0.57(0.65)	PA vs NFB	0.08	(-0.37, 0.52)	.729	0.28	(-0.16, 0.73)	.211	.357
	PA	17	1.03(0.50)	17	0.86(0.79)	17	0.73(0.86)								
SWAN-H/I	NFB	20	1.30(0.67)	20	0.85(0.72)	20	0.56(0.66)	MPH vs NFB	-0.37	(-0.76, 0.02)	.058	0.07	(-0.32, 0.45)	.734	.011
	MPH	21	1.03(0.52)	21	0.32(0.70)	21	0.47(0.63)	PA vs NFB	0.02	(-0.40, 0.43)	.936	0.16	(-0.25, 0.57)	.435	.411
	PA	17	0.90(0.83)	17	0.62(0.88)	17	0.48(0.94)								
Teacher ratings															
SDQ	NFB	20	14.50(4.36)	20	14.25(3.60)	20	11.25(5.80)	MPH vs NFB	-5.15	(-8.36, -1.93)	.002	-1.24	(-4.45, 1.97)	.445	.028
	MPH	21	12.71(3.62)	21	8.38(4.81)	21	9.29(6.02)	PA vs NFB	1.37	(-2.14, 4.90)	.441	3.84	(0.37, 7.31)	.030	.205
	PA	16	15.44(4.02)	14	15.93(5.55)	16	16.06(5.81)								
SWAN-IN	NFB	20	1.27(0.98)	20	1.18(0.84)	20	0.60(1.16)	MPH vs NFB	-1.06	(-1.54, -0.58)	<.001	-0.43	(-0.91, 0.05)	.078	.019
	MPH	21	1.52(0.67)	21	0.27(0.71)	21	0.30(1.04)	PA vs NFB	-0.15	(-0.70, 0.38)	.565	0.56	(0.04, 1.08)	.036	.017
	PA	16	1.30(0.70)	14	1.03(0.65)	16	1.17(0.80)								
SWAN-H/I	NFB	20	1.19(0.91)	20	0.96(1.26)	20	0.37(1.12)	MPH vs NFB	-0.81	(-1.34, -0.30)	.003	-0.17	(-0.70, 0.35)	.517	.020
	MPH	21	0.93(1.32)	21	0.00(0.77)	21	0.05(0.88)	PA vs NFB	0.24	(-0.34, 0.82)	.404	0.73	(0.16, 1.30)	.013	.110
	PA	16	0.85(0.83)	14	1.06(1.03)	16	0.95(0.97)								
Neurocognitive otcome measures															
Stop-signal task															
SSRT	NFB	19	269.31(93.38)	18	247.55(100.17)	18	208.45(80.83)	MPH vs NFB	-63.09	(-105.86, -20.31)	.004	-36.22	(-79.33, 6.90)	.098	.188
	MPH	19	280.33(95.82)	19	191.52(78.13)	18	176.64(94.35)	PA vs NFB	0.04	(-45.13, 46.00)	.986	28.76	(-16.18, 73.70)	.206	.177
	PA	17	219.07(64.33)	16	211.45(78.27)	17	210.40(70.43)								
Commission	NFB	19	19.42(13.70)	18	19.00(14.53)	18	15.33(11.78)	MPH vs NFB	-7.40	(-14.93, 0.12)	.054	-4.91	(-12.50, 2.69)	.202	.479
	MPH	19	22.11(11.40)	19	13.15(9.80)	18	13.83(17.23)	PA vs NFB	3.24	(-4.60, 11.07)	.412	4.36	(-3.37, 12.10)	.265	.757
	PA	17	16.29(9.58)	16	20.19(13.38)	17	19.24(15.32)								
	NFB	19	13.37(13.55)	18	15.94(15.89)	18	11.06(12.30)	MPH vs NFB	-9.31	(-15.45, -3.16)	.003	-6.33	(-12.55, -0.11)	.046	.467

Omission														
	MPH	19	12.89(10.67)	19	5.79(8.04)	18	5.10(6.25)	PA vs NFB	0.57	(-5.85, 7.00)	.861	4.41	(-1.90, 10.73)	.169	.363
	PA	17	12.41(10.17)	16	14.94(12.34)	17	16.00(14.68)								
MRT	NFB	19	622.20(154.01)	18	610.61(149.32)	18	563.45(130.50)	MPH vs NFB	-31.50	(-99.40, 36.43)	.359	-7.26	(-75.92, 61.40)	.834	.484
	MPH	19	654.41(101.32)	19	589.02(135.22)	18	578.90(127.80)	PA vs NFB	19.54	(-51.15, 90.23)	.584	43.42	(-26.64, 113.50)	.221	.503
	PA	17	659.35(108.89)	16	639.78(138.97)	17	632.19(117.26)								
CV	NFB	19	0.27(0.05)	18	0.28(0.05)	18	0.28(0.05)	MPH vs NFB	-0.03	(-0.06, <0.01)	.063	-0.02	(-0.05, 0.01)	.132	.736
	MPH	19	0.28(0.03)	19	0.25(0.05)	18	0.26(0.05)	PA vs NFB	<-0.01	(-0.03, 0.03)	.881	0.01	(-0.02, 0.03)	.731	.634
	PA	17	0.27(0.04)	16	0.27(0.03)	17	0.29(0.04)								
VSWM															
Forward	NFB	20	12.45(2.89)	20	13.40(3.58)	19	14.32(3.30)	MPH vs NFB	0.63	(-0.83, 2.10)	.395	0.78	(-0.70, 2.25)	.293	.825
	MPH	21	10.52(2.62)	21	12.57(2.79)	21	13.76(3.32)	PA vs NFB	-0.52	(-2.04, 1.00)	.494	-1.21	(-2.73, 0.32)	.119	.357
	PA	17	11.06(2.63)	17	11.82(2.65)	17	12.18(2.38)								
Backward	NFB	39	10.90(3.08)	38	11.68(3.44)	33	11.42(3.62)	MPH vs NFB	1.06	(-0.18, 2,30)	.093	0.93	(-0.36, 2.22)	.158	.843
	MPH	36	9.58(2.45)	31	11.71(3.66)	28	11.82(3.53)	PA vs NFB	0.17	(-1.04, 1.38)	.784	0.43	(-0.83, 1.70)	.497	.687
	PA	37	9.95(2.95)	34	10.76(3.32)	31	11.26(3.56)								
Side effects															
SDSC	NFB	19	44.21(9.38)	20	42.50(8.47)	20	43.10(8.33)	MPH vs NFB	0.12	(-4.01, 4.26)	.952	-0.65	(-4.74, 3.43)	.751	.731
	MPH	20	43.90(8.75)	20	42.05(10.10)	20	41.40(7.80)	PA vs NFB	1.27	(-3.31, 5.85)	.583	0.06	(-4.62, 4.73)	.981	.632
	PA	15	50.40(14.97)	15	49.73(12.84)	15	49.33(12.85)								

Note: Neurofeedback was used as a reference group to compare intervention effects with stimulant medication (MPH versus NFB) and physical activity (PA versus NFB). M=Mean; SD=Standard Deviation; SDQ=Strength and Difficulty Questionnaire; SWAN=Strengths and Weaknesses in ADHD and Normal Behaviors; H/I=Hyperactivity/Impulsivity scale; MRT=mean reaction time; CV=coefficient of variation; SSRT=stop-signal reaction time; VSWM=visual spatial working memory; SDSC=Sleep Disturbance Scale for Children.

Chapter 5

A 6-month follow-up of neurofeedback treatment in children with ADHD exploring effects on EEG power spectra

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Abstract

Objective: Neurofeedback has been proposed as an effective alternative for pharmacological treatment in children with ADHD, with potentially long-term benefits. However, the specificity of the reported beneficial effects is controversial and the need for additional research into the neurophysiological effects of neurofeedback has been emphasized. We compared long-term effects of neurofeedback (NFB) to methylphenidate (MPH) and physical activity (PA, a semi-active control intervention) on electroencephalogram (EEG) power spectra.

Method: A follow-up of a randomized controlled trial into the effects of NFB, MPH and PA was conducted. EEG power spectra measures of theta, alpha and beta activity, during resting and task conditions, were recorded at pre-, post-intervention and follow-up in 67 children, aged 7-13 (NFB: n=24, MPH: n=23, or PA: n=20).

Results: Analyses revealed no EEG power spectra differences at follow-up during resting and active task conditions between MPH and NFB (range p=.165 to .905) and PA and NFB (range p=.172 to .822).

Conclusions: At six-month follow-up, EEG power spectra of all three interventions came closer together over time without one intervention being superior to another.

Significance: This study is the first to indicate that neurofeedback has no specific long-term effects nor specific delayed effects compared to MPH and PA.

Introduction

ADHD is a childhood onset neurodevelopmental disorder characterized by persistent symptoms of inattention, hyperactivity and impulsivity.[1] Stimulant medication is effective and widely used for the treatment of ADHD.[2] However, the use of stimulant medication can have adverse side effects[3] and there is limited evidence for long-term effects.[4] Moreover, effects of stimulant medication disappear immediately after the treatment is ended. Neurofeedback has been proposed as a non-pharmacological alternative treatment for ADHD[5] that may have long-term effects. Neurofeedback is used to alter brain activity by presenting real-time feedback of electroencephalogram (EEG) activity to the patient. Although neurofeedback seems to improve ADHD symptoms, there is much debate on whether these effects are specifically mediated by altering brain function. Specificity can be investigated with sham-controlled randomized controlled trial (RCT) designs,[6] or by exploring short and long-term effects of neurofeedback on the electrophysiology of the brain. Although some randomized controlled trial (RCT) studies have been conducted on short-term electrophysiological effects,[7-9] no such studies have yet been done for long-term electrophysiological effects.

It has been shown that children with ADHD have increased theta (4-8Hz) and decreased beta (13-20Hz) compared to typically developing children.[10] Therefore, an often-used neurofeedback protocol focuses on decreasing the theta/beta ratio in children with ADHD. Results of meta-analyses on the efficacy of neurofeedback in children with ADHD are inconsistent.6,[11-13] The most recent meta-analysis of Cortese et al.[14] could not demonstrate the efficacy of neurofeedback on probably blinded outcomes and studies with a high-quality control arm (sham or active), questioning the specificity of neurofeedback effects in most studies.

To get more insight into the specificity of neurofeedback, it has been suggested to investigate both short term (during a training session and over de course of training sessions) and sustainable (persisting after cessation of the training sessions) EEG changes induced by neurofeedback. In addition, it has been recommended to identify the relation between these (short-term and sustainable) EEG changes and clinical outcomes in children with ADHD.[15] Data on training short term EEG changes induced by neurofeedback have not frequently been reported and results show inconsistent outcomes.[16-18] Results are mixed in terms of learning effects (absent/present), the direction of the reported effects (desired/opposite) and also frequency bands. Moreover, overall learning effects induced by theta/beta neurofeedback did not seem be associated with behavioral outcomes measured at post-intervention.[19,20,18]

Results of RCT studies investigating sustainable effects of neurofeedback on power spectra (persisting after cessation of the training sessions) are also mixed.[7-9] The RCT study of Ogrim and

Hestad[9] comparing neurofeedback and stimulant medication, found superior behavioral effects for stimulant medication compared to neurofeedback. The authors revealed no changes in power spectra in either intervention. In contrast, Gevensleben et al.[7] found neurofeedback to improve behavior, which in turn was related to decreased theta activity in the resting EEG. It should be mentioned that these findings were not protocol specific, as the study used a combination of theta/beta and slow-cortical potential training. Nonetheless, these results were replicated by our group,[8] solely using a theta/beta protocol. To be more specific, Janssen et al.[8] found a similar decrease from pre- to post-intervention in theta power during resting EEG for both neurofeedback and stimulant medication, compared to a semi-active control intervention. These findings suggest that the effects on theta power are not specifically related to neurofeedback, but also emerge with stimulant medication treatment. Interestingly, both Janssen et al.[8] and Gevensleben et al.[7] found higher baseline theta power at pre-intervention to be predictive of ADHD-symptom reduction from pre- to post-intervention and greater theta power changes were predictive of greater ADHD-symptom reductions from pre- to post-intervention. However, in contrast to Gevensleben et al.,[7] neurofeedback did not have any beneficial effects on behavior, when compared to both stimulant medication and physical activity.[21] Therefore, the specificity of neurofeedback remains unclear.

To our knowledge there are no follow up studies on RCT's that provide insight into possible long-term effects of neurofeedback on EEG power spectra. Arns and Kenemans[22] have described a model in which delayed behavioral and electrophysiological effects of neurofeedback may be expected. Their model is based on findings of sleep onset insomnia (SOI) in an ADHD sub-group. They argued that neurofeedback might have an impact on the sleep spindle circuitry, resulting in increased sleep spindle density, in turn normalizing sleep onset insomnia (SOI) and thereby affecting the noradrenergic locus coeruleus to finally result in vigilance stabilization. Normalization of SOI would cause delayed reductions of ADHD symptoms along with reduced frontal theta and alpha power. In the current six-month naturalistic follow-up study, we compared neurofeedback with stimulant medication (methylphenidate) and physical activity as a semi-active control group, in terms of their long-term effects on EEG power spectra (theta, alpha and beta) during eyes closed (EC), eyes open (EO) and active task conditions.

Methods

Participants

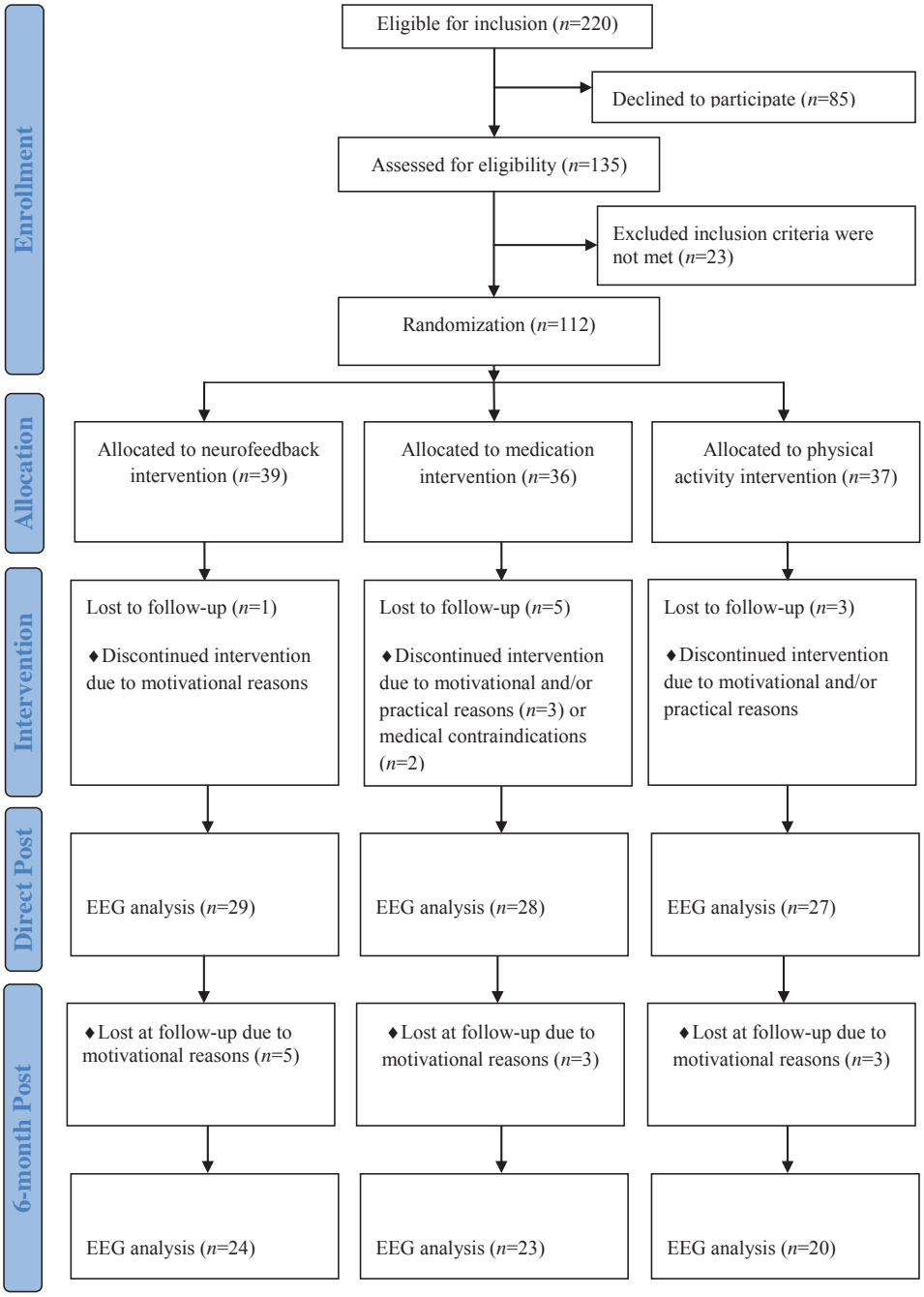
Eligible participants were Dutch speaking children, 7-13 years, with a primary clinical DSM-IV-TR diagnosis of ADHD.[1] Children with ADHD were recruited from fifteen child mental health

outpatient care facilities in the west of the Netherlands. Before entering the study, parent- and teacher ratings on the Disruptive Behavior Disorders Rating Scale (DBDRS)[23] confirmed their diagnosis; at least one of the scores on the Inattention or Hyperactivity/Impulsivity scales had to be above the 90th percentile for one of the informants, and above the 70th percentile for the other informant (signifying pervasiveness of symptoms). At study entry, all children were free of stimulant use for at least one month. Exclusion criteria were neurological disorders and IQ below 80 as measured by a four subtest version of the Wechsler Intelligence Scale of Children-III (WISC-III) including the subtests Vocabulary, Arithmetic, Block Design, and Picture Arrangement.[24] No restrictions were set on other comorbidities. Comorbid disorders were diagnosed according to DSM-IV-TR and retrieved from the diagnostic reports of the participants' clinicians. Comorbid disorders included learning disorders (NFB; n=5, MPH; n=2, PA; n=1), autism spectrum disorders, (NFB; n=3, MPH; n=2, PA; n=3), anxiety disorders (NFB; n=2, MPH; n=0, PA; n=2), and mood disorder (NFB; n=1, MPH; n=0, PA; n=0). Chi-square test revealed no significant difference in the distribution of comorbid disorders over groups (χ^2 (8, N=112)=12.88, p=.12).

Initially, 112 children with ADHD were randomized over the three interventions: NFB (n=39), MPH (n=36) or PA (n=37). At six-month follow-up, the total drop out did not differ between groups; NFB, n=6 (15.4%) or MPH, n=8 (22.2%) or PA n=6 (16.2%), p=.705 two-tailed Fisher's exact test. In total, 92 children, NFB (n=33), MPH (n=28) or PA (n=31), participated in the six-month follow-up measurement. Figure one presents a flow diagram of participants.

EEG power spectra measures during eyes open (EO), eyes closed (EC) and task (effortful) conditions were available for 97 children at pre-intervention (NFB, n=33, MPH n=33, PA n=31). For 15 subjects data needed to be discarded due to poor data quality. We adjusted our analyses of EEG power spectra for pre-intervention power spectra (here referred to as 'baseline'), therefore, only participants with baseline were analyzed. In other words, if pre-intervention data was poor, post-intervention and follow-up data were also excluded from analyses. At post-intervention, EEG power spectra measures were available for 84 children (NFB, n=29, MPH n=28, PA n=27). Missing data were due to data quality at baseline (n=11), poor post-intervention data quality (n=7), or motivational problems (n=1). At follow-up, EEG power spectra measures were available for 67 children (NFB, n=24, MPH n=23, PA n=20). Missing data were due to data quality at baseline (n=12) and poor follow-up data quality (n=13). Figure 1 presents a flow diagram of participants.

Figure 1. Flow diagram randomized controlled trial.



Trial design

A multicentre three-way parallel group study with balanced randomization was conducted. A randomization table was created using a computerized random number generator.[25] Stocks of nine unmarked sealed envelopes were presented to parents at intake. Parents randomly picked an envelope revealing intervention allocation. Subsequently, children, parents, and teachers were aware of the allocated group. Data collection took place between September 2010 and March 2014. A full description of power analyses based on behavioral data can be found in Geladé et al.,[21] neurophysiological data were considered secondary outcome measures. The trial was registered on clinicaltrials.gov (Ref. No. NCT01363544).

Interventions

NFB and PA treatment consisted of three individual training sessions a week, with each session lasting 45 minutes including 20 minutes of effective training, over a period of 10-12 weeks. All interventions, as described below, took place after the pre-intervention assessment. A full description of the interventions can be found in Geladé et al.[21]

Neurofeedback (NFB). Theta/beta training was applied with the aim to inhibit theta (4-8Hz) and reinforce beta (13-20Hz) activity at Cz. Theta/beta index was represented to the participant by simple graphics on a screen. Successful reduction of the theta/beta index as averaged over one trial relative to session baseline, was rewarded with the appearance of a sun and granted with credits. To promote generalization of the learned strategies into daily life, transfer trials were used. The mean number of training sessions of participants who completed the assessments at post intervention (n=38) was 29 (M=28.53, SD=2.63, range between 19-30). The mean number of training sessions of participants who completed the assessments at follow-up (n=33) was 29 (M=28.94, SD=1.75, range between 22-30). The mean number of training sessions of participants who completed the assessments at follow-up and had EEG power spectra measures available (n=24) was 29 (M=28.75, SD=1.92, range between 22-30). Of this group , 9 children were using medication while 15 children were not.

Methylphenidate (MPH). After the pre-intervention assessment, a four-week double-blind randomized placebo-controlled titration procedure was used to determine the optimal individual dose of short-acting methylphenidate (MPH).[26] In total, 31 children completed the titration procedure. Children were classified by a standardized procedure[27] as responders when their ADHD symptoms significantly decreased compared to placebo (n=29). The two non-responders were treated with 5mg MPH twice daily. The child's psychiatrist prescribed the optimal dose for the

remaining intervention period (5mg to 10 children including 8 responders and 2 non-responders, 10mg to 14 children, 15mg to 2 children, and 20mg to 5 children). At follow-up, 21 children were using medication while 7 children discontinued medication usage. Of the children who completed follow-up and had EEG power spectra available, 17 children were using medication while 6 children discontinued medication usage.

Physical activity (PA) as semi-active control condition. Each training session started with 5 minutes of warming up, followed by five 2-minute moderate intensity exercises at a level of 70-80% of HRmax. After a 5-minute break, five 2-minute vigorous intensity exercises of 80-100% of HRmax were performed. Time and heart rate were monitored and registered using a POLAR FT4 watch (Polar Electro Oy, Kempele, Finland). The mean number of sessions of participants who completed the assessments at post intervention (n=34) was 28 (M=27.74, SD=3.56, range 12-30). The mean number of training sessions of participants who completed the assessments at follow-up (n=31) was 28 (M=28.29, SD=2.30, range between 19-30). The mean number of training sessions of participants who completed the assessments at follow-up and had EEG power spectra measures available (n=20) was 28 (M=28.25, SD=2.63, range between 19-30). Of this group, 9 children were using medication while 11 children were not.

Behavioral Outcome Measures

Behavioral outcome measures included parent and teacher reports on the Strengths and Weaknesses of ADHD symptoms and Normal behavior scale[26] (SWAN). Both the SWAN scales of Inattention and Hyperactivity/Impulsivity were assessed.

Electrophysiological Outcome Measures

EEG recording started with 3 minutes eyes open (EO) and 3 minutes eyes closed (EC) resting conditions, followed by a task condition involving the stop-signal task (SST). A full description of the SST can be found in Janssen et al.[28]

Electrophysiological recordings. Continuous EEG was recorded at 512Hz using the Active Two Biosemi system and ActiView software (Biosemi, Amsterdam, The Netherlands) from 128 scalp electrodes according to the ABC labeling system, referenced to the active common mode and grounded to the passive right leg, which functions as a feedback loop to drive average potentials across electrodes to the amplifier zero. The electro-oculogram (EOG) was obtained using two electrodes at the external canthi, and two electrodes at infra- and supra-orbital sides. Reference electrodes were placed at both mastoids.

Off-line analysis was performed with Brain Vision Analyzer 2 software (Brain Products, Gilching, Germany). The sampling rate was down-sampled to 256Hz and scalp electrodes were re-referenced to the average of the mastoids. Data were band-pass filtered at 0.1-30Hz at 24 dB/oct and a 50-Hz notch filter was applied. Ocular artefacts were corrected with the method of Graton & Coles.29 The continuous EEG was segmented in 2-second intervals and automatic artifact rejection was applied to segments with amplitudes exceeding +/- 100μV. At least 30 artefact-free segments were required for EC, EO, and task conditions for further analysis. The remaining segments were Fast Fourier-transformed and averaged. Mean power was calculated for theta (4-8Hz), alpha (8-12Hz) and beta (13-20Hz) frequency bands at midline electrodes (Fz, Cz, Pz).

Procedure

The study was approved by the national medical ethics committee (NL 31641.029.10 CCMO). Written informed consent was obtained before participation from all parents and children aged 11 years and older.

Pre-intervention assessment took place in the week prior to the start of the intervention. Post-intervention assessment took place one week after the last training. At follow-up, six months after post-intervention, the assessment included similar measurements to prior assessments. Post-intervention effects have been reported previously, evaluating effects of neurofeedback on behavioral outcomes, cognitive functioning, event-related potentials and EEG power spectra.[8,21,30,31] During post-intervention assessment, the MPH-group continued use of medication. Interventions took place between September 2010 and March 2014. The six-month follow-up was naturalistic and children were allowed to start, continue or stop interventions, including the use of stimulant-medication.

Statistical methods

Statistical analyses were performed with IBM SPSS Statistics, version 20.0.[32] Differences between intervention groups in terms of background characteristics were analyzed by means of a chi-square test (χ^2) or one-way ANOVA with Tukey post-hoc analyses to compare intervention groups. Attrition analysis was performed with ANOVA and a chi-square test (χ^2) by comparing the total sample with the EEG subsample on group characteristics, and by exploring possible interactions with treatment group. To obtain normally distributed data, power spectra measures were log10 transformed. Intervention effects were analyzed with linear mixed models. Mixed models were used because the outcome at post-intervention and follow-up were clustered within

subjects. Separate models were used for each condition (EC, EO, task) and frequency band (theta, alpha, beta). In the model, within-subject factor Time (post-intervention and follow-up) and location (Fz, Cz, Pz), between-subject factor Group and the interaction Time x Group were added, while adjusting for baseline values and age. EEG power spectra is known for change during maturation;33 therefore, age was inserted as covariate in all analyses. Intervention effects were analyzed by comparing neurofeedback to stimulant medication (MPH versus NFB) and physical activity (PA versus NFB). Comparison of groups are reported by mean difference (MD) and 95% confidence intervals [95%CI]. Results were considered significant at $p \leq .05$.

Because children were allowed to start, continue or stop stimulant medication use during the follow-up interval, we performed sensitivity analyses adjusting for medication use at follow-up in the neurofeedback and physical activity group.

To explore the relation of EEG changes to clinical outcomes, Pearson correlations were calculated between (1) difference scores of parents- and teacher-rated SWAN Inattention and Hyperactivity/impulsivity scores (follow-up – post-intervention) and (2) difference scores of EEG change in power (follow-up – post-intervention). Pearson correlations were computed within groups and age effects were adjusted in all analyses. Only significant correlations of ≤ .01 are reported.

Results

Group characteristics

Group characteristics are displayed in Table 1. Analyses of group characteristics showed no difference between groups, except for medication use at follow-up ($p < .05$). Post-hoc tests showed less stimulant medication use at follow-up in the NFB and PA group compared to the MPH group.

Table 1. Group characteristics

	NFB (*n*=33)		MPH (*n*=28)		PA (*n*=31)		Group	
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*
Age (years)	9.81	1.86	8.97	1.22	9.55	1.76	1.98	ns
IQ	100.88	13.84	102.14	14.90	98.94	12.91	0.40	ns
Gender, (M/F)	24/9		22/6		24/7		0.33[a]	ns
Stimulant medication at T2 (On/Off)	12/20		21/7		14/17		8.70	.01
Parent rating								
DBDRS								
Inattention	16.58	5.12	16.00	5.71	16.00	5.00	0.13	ns
H/I	13.73	5.84	12.50	5.75	12.97	6.24	0.33	ns
Teacher rating								
DBDRS								
Inattention	15.76	5.27	17.00	6.44	15.26	5.68	0.70	ns
H/I	13.90	7.00	12.11	9.64	12.32	7.42	0.46	ns

Note. DBDRS=Disruptive Behavior Disorder rating scale; H/I=Hyperactivity/Impulsivity scale; M=Mean; SD=Standard Deviation; [a]$\chi(2)$; y=years.

Attrition analyses

Group characteristics did not differ between the initially randomized sample and the EEG subsample, nor were there any interaction with treatment group.

EEG outcome measures

Table 2 shows the log transformed EEG power spectra of the theta, alpha, and beta frequency bands at pre-, post-intervention and follow-up as well as the results of the mixed model analyses for the three conditions (EC, EO, task). Sensitivity analyses, considering medication use at follow-up, are presented at Supplementary Table 1.

Eyes closed condition. For the theta band, the time by group interaction was not significant for the MPH and NFB group contrast, nor did the two groups differ at follow-up. A significant time by group interaction was found for the PA and NFB group contrast (p=.020): in the PA group slight reductions were observed in theta power from post-intervention to follow-up, while theta power marginally increased from post-intervention to follow-up in children that had received NFB. However, post-intervention and follow-up results for theta EC did not differ between the two groups.

For the alpha band, a significant time by group interaction was found for the MPH and NFB group contrast (p=.024): the NFB group showed a slightly larger increase of alpha power from post-intervention to follow-up compared to the children in the MPH group. However, post-

intervention and follow-up results for alpha EC did not differ between the two groups. For the PA and NFB group contrast, a significant time by group interaction was also found (p=.012): alpha was stable from post-intervention to follow-up in the PA group, while the NFB group showed a slight increase of alpha power. However, the two groups did not differ post-intervention and at follow-up. For the beta band, no significant time by group effects were found and no significant group differences were found at the follow-up.

Eyes open condition. For the theta band, the MPH and NFB group contrast showed no significant time by group effect, nor did the two groups differ at follow-up. The time by group interaction was significant for the PA and NFB group contrast (p=.003): the PA group showed a decrease in theta power from post-intervention to follow-up, while children in the NFB group showed stable theta power levels across the two assessments. However, post-intervention and follow-up results for theta EO did not differ between the two groups. For the alpha and beta band, no significant time by group effects were found and no significant group differences were found at the follow-up.

Task condition. For the theta band, the MPH and NFB group contrast showed no significant time by group effect, nor did the two groups differ at follow-up. For the PA and NFB group contrast, a significant time by group interaction was found (p=.004): both groups showed decreasing levels of theta power; however, the level of theta power decreased more in children in the PA group compared to the children in the NFB group. However, the two groups did not differ post-intervention and at follow-up. For the alpha and beta band, no significant time by group effects were found and no significant group differences were found at the follow-up.

When medication use at follow-up was inserted as a covariate into our analyses, results remained unchanged, with a single exception. For alpha in the task condition, the time by group interaction for the PA and NFB group contrast just escaped conventional levels of significance (p=.059) but after adjusting for medication use at follow-up, the group contrast became significant (p=.012): children in the PA group showed a somewhat more pronounced reduction in alpha power compared to the NFB group from post-intervention to follow-up. However, results post-intervention and at follow-up remained unchanged compared to main analyses.

Relation between EEG and behavior. We explored the relation between EEG changes and changes in clinical outcomes assessed with parent and teacher ratings on the Inattention and Hyperactivity/Impulsivity scale of the SWAN. These analyses were conducted separately in the three intervention groups. None of the findings involving teacher rating reached significance. In the MPH group, reductions in theta power from post-intervention to follow-up in the eyes closed

condition were associated with improvements in parent rated hyperactive/impulsive behavior, $r(19) = 0.563$, $p = 0.008$. Further, in the PA group, reductions in beta power in the eyes closed condition from post-intervention to follow-up were associated with worsening of parent rated inattention problems, $r(14) = -0.730$, $p = 0.001$. Likewise, in the PA group, reductions in beta power in the eyes closed condition from post-intervention to follow-up were associated with worsening of parent rated hyperactive/impulsive behavior, $r(14) = -0.687$, $p = 0.003$.

Table 2. Analyses of outcome measures

		Pre-intervention		Post-intervention		Follow-up		Group Contrasts	Difference at Post-intervention			Difference at Follow-up			Time* Group
		n	*M* (*SD*)	*n*	*M* (*SD*)	*n*	*M* (*SD*)		beta	95% *CI*[3]	*p*	beta	95% *CI*	*p*	*p*
Theta EC[1]															
	NFB	33	.655(.266)	29	.590(.293)	24	.603(.253)	MPH vs NFB	-0.03	(-0.10, 0.04)	.352	-0.05	(-0.12, 0.02)	.165	.432
	MPH	33	.658(.170)	28	.572(.147)	23	.570(.169)	PA vs NFB	0.04	(-0.03, 0.11)	.318	-0.02	(-0.09, 0.05)	.592	.020
	PA	31	.624(.220)	27	.599(.224)	20	.589(.222)								
Alpha EC															
	NFB	33	.620(.301)	29	.560(.332)	24	.591(.313)	MPH vs NFB	0.05	(-0.05, 0.14)	.318	-0.02	(-0.11, 0.08)	.717	.024
	MPH	33	.603(.302)	28	.560(.300)	23	.573(.337)	PA vs NFB	0.05	(-0.05, 0.14)	.324	-0.03	(-0.12, 0.07)	.559	.012
	PA	31	.553(.310)	27	.528(.343)	20	.532(.340)								
Beta EC															
	NFB	33	-.340(.155)	29	-.364(.183)	24	-.352(.187)	MPH vs NFB	0.02	(-0.04, 0.07)	.553	0.02	(-0.04, 0.07)	.573	.993
	MPH	33	-.329(.200)	28	-.348(.205)	23	-.348(.215)	PA vs NFB	0.01	(-0.04, 0.07)	.700	0.02	(-0.04, 0.08)	.555	.761
	PA	31	-.369(.214)	27	-.413(.188)	20	-.396(.201)								
Theta EO[2]															
	NFB	33	.505(.223)	29	.455(.225)	24	.458(.217)	MPH vs NFB	-0.02	(-0.08, 0.04)	.490	<-0.01	(-0.06, 0.06)	.905	.408
	MPH	33	.546(.151)	28	.477(.141)	23	.500(.150)	PA vs NFB	0.03	(-0.03, 0.09)	.257	-0.03	(-0.09, 0.03)	.345	.003
	PA	31	.475(.170)	27	.472(.160)	20	.426(.132)	PA vs MPH							
Alpha EO															
	NFB	33	.291(.251)	29	.246(.278)	24	.258(.248)	MPH vs NFB	0.02	(-0.06, 0.10)	.641	0.05	(-0.04, 0.13)	.253	.268
	MPH	33	.311(.257)	28	.249(.262)	23	.326(.300)	PA vs NFB	0.05	(-0.02, 0.13)	.199	0.01	(-0.07, 0.10)	.747	.154
	PA	31	.204(.232)	27	.210(.283)	20	.202(.254)	PA vs MPH							
Beta EO															
	NFB	33	-.400(.162)	29	-.443(.183)	24	-.414(.181)	MPH vs NFB	0.04	(-0.02, 0.09)	.217	0.02	(-0.04, 0.08)	.436	.480
	MPH	33	-.377(.200)	28	-.406(.200)	23	-.404(.196)	PA vs NFB	0.02	(-0.03, 0.08)	.418	0.01	(-0.05, 0.07)	.822	.366
	PA	31	-.457(.220)	27	-.496(.204)	20	-.480(.232)	PA vs MPH							
Theta task															
	NFB	33	.590(.202)	29	.555(.226)	24	.537(.230)	MPH vs NFB	-0.05	(-0.10, 0.01)	.088	-0.02	(-0.08, 0.03)	.455	.233
	MPH	33	.658(.169)	28	.573(.141)	23	.580(.158)	PA vs NFB	0.02	(-0.03, 0.08)	.360	-0.04	(-0.09, 0.02)	.172	.004
	PA	31	.577(.182)	27	.567(.155)	20	.502(.155)	PA vs MPH							
Alpha task															
	NFB	33	.216(.229)	29	.191(.262)	24	.173(.211)	MPH vs NFB	-0.04	(-0.10, 0.02)	.205	-0.01	(-0.08, 0.05)	.721	.202
	MPH	33	.280(.220)	28	.186(.170)	23	.222(.228)	PA vs NFB	0.03	(-0.03, 0.09)	.380	-0.02	(-0.08, 0.05)	.631	.059

	PA	31	.157(.254)	27	.153(.287)	20	.110(.221)	PA vs MPH						
Beta task														
	NFB	33	-.410(.151)	29	-.400(.172)	24	-.391(.155)	MPH vs NFB	-0.02	(-0.07, 0.04)	.519	-0.01	(-0.06, 0.05)	.827	.515
	MPH	33	-.345(.214)	28	-.388(.204)	23	-.383(.206)	PA vs NFB	<-0.01	(-0.06, 0.05)	.949	0.01	(-0.05, 0.07)	.732	.528
	PA	31	-.440(.231)	27	-.464(.213)	20	-.454(.227)	PA vs MPH						

Note. EC[1]=eyes closed; EO[2]=eyes open, CI[3]=Confidence Interval.

Discussion

Much debate has focused on whether the effects induced by neurofeedback are specifically mediated by altered brain function. In the current study, we examined the specificity of neurofeedback by exploring long-term electroencephalogram (EEG) changes. To the best of our knowledge, our study is the first RCT exploring long-term effects on EEG power spectra in children with ADHD. More specifically, we compared neurofeedback with stimulant medication and physical activity - as a semi-active control group - in terms of their effects on measures of EEG power spectra at six-month follow-up. While at post-intervention, we found a comparable reduction in theta power during resting EEG (eyes open) in both the neurofeedback and stimulant medication group as compared to the semi-active control group,[8] at follow-up, no group differences were found on any of the power spectra, even when analyses adjusted for medication effects. The present follow-up data, therefore, do not support long-term specificity of neurofeedback.

One of our previous studies, investigating long-term behavioral and neurocognitive effects of neurofeedback, showed that, at follow-up, children who had received neurofeedback catched-up with their peers who had received methylphenidate.[34] Moreover, at follow-up, teacher ratings showed improved behavior in children who received neurofeedback compared to children in the semi-active control group. These findings, together with the predictions based on the model proposed by Arns & Kenemans,[22] called attention on the possibility of delayed effects of neurofeedback in children with ADHD, and encouraged us to explore long-term neurophysiological effects of neurofeedback in the current study. We found, however, no specific neurophysiological effects of neurofeedback. Moreover, the present findings showed some evidence for beneficial effects of the semi-active control condition as compared to the neurofeedback intervention on theta and alpha power, although differences were not significant at follow-up. In sum, it seems that at follow-up our groups came closer together over time without one group being superior to another. These findings are in accordance with long-term behavioral effects reported by parents[21] and the results reported for the effects of neurofeedback on neurocognitive measures.[34,35]

In addition, we explored the relation between the EEG power spectra changes and both parent and teacher reported behavioral outcomes assessed at follow-up. Previously, our group8 replicated findings of Gevensleben et al.,[7] who reported a significant association between pre- to post-intervention reductions in theta power and improved ADHD-related behavioral outcome measures with neurofeedback. The present study found no significant relationship between the EEG power spectra changes and changes in behavioral outcomes from post-intervention to follow-up in the neurofeedback group. Significant associations between changes in behavioral and

neurophysiological measures were obtained for children in the stimulant medication intervention and semi-active control intervention. In children who received stimulant medication, reduced theta was associated with improved parent reported hyperactivity/impulsivity. In contrast to our results, Loo et al.[36] found decreased theta to be associated with improved attention and increased beta to be associated with better functioning in both attention and hyperactivity domains. The current study, however, did not find a significant association between beta activity and any of the behavioral measures. Finally, in the physical activity group, reduced beta power was associated with increased parent reported inattention and hyperactivity/impulsivity. Although, the latter association is in accordance with earlier results,[10] correlations in all three intervention groups should be interpreted with great caution as groups were small and therefore did not allow us to adjust for stimulant medication use at follow-up.

The present study, is to our knowledge the first study to explore long-term effects of neurofeedback on neurophysiological outcome measures. Our longitudinal hierarchical multilevel model analyses, corrected for possible age effects[33] and also accounted for pre-intervention differences in EEG power spectra measures. In addition, we conducted sensitivity analyses to control for stimulant medication use during the follow-up assessment. These analyses revealed no fundamental change of our main results. Despite these strengths, this study also has some limitations. First, while previous studies have reported effects of stimulant medication on theta power,[37,38] alpha power[39,40] and beta power,[41] we found no such effects compared to the other interventions. A closer look at our power spectra data shows large variability in the EEG power spectra measures, especially for the alpha measures. This might have contributed to the fact that we did not find any evidence for stimulant mediated changes in the power spectra. Theta power, however, seemed less variable and although post-intervention assessment showed stimulant treatment to enhance theta,[8] these effects did not persist at follow-up. Obviously, the current study limited by the use of a naturalistic follow-up design. Unmeasured and/or unexamined confounding variables could have interfered with the current findings and might have led to masking of potential small effects. To detect these small effects, larger samples are needed.

Conclusion

Previous findings of our group showed that neurofeedback resulted in specific neurophysiological effects, i.e., reduced theta power, as measured post intervention.[8] Adding to the evidence for the specificity of neurofeedback, teacher reports revealed improved behavior in children who received neurofeedback compared to the semi-active control group at six-month follow-up.[34] The current

study explored long-term concomitant EEG power effects at six-month follow-up comparing neurofeedback to stimulant medication and a semi-active control intervention. Although for some conditions and power bands, significant time by group interactions emerged, none of the group comparisons on the post-intervention and follow-up assessment data were significant. We did not find any difference between groups at follow-up, and therewith failed to find evidence supporting the specificity of neurofeedback. These results are in accordance with our long-term behavioral parent reports and neurocognitive functioning, indicating no difference between all three groups at follow-up.[34]

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Supplementary Table 1. Sensitivity analyses of outcome measures

		Pre-intervention		Post-intervention		Follow-up		Group Contrasts	Difference at Post-intervention			Difference at Follow-up			Time* Group
		n	*M*(*SD*)	*n*	*M*(*SD*)	*n*	*M*(*SD*)		beta	95% *CI*[3]	*p*	beta	95% *CI*	*p*	*p*
Theta EC[1]															
	NFB	33	.655(.266)	29	.590(.293)	24	.603(.253)	MPH vs NFB	-0.03	(-0.10, 0.04)	.356	-0.05	(-0.12, 0.03)	.202	.535
	MPH	33	.658(.170)	28	.572(.147)	23	.570(.169)	PA vs NFB	0.04	(-0.03, 0.11)	.317	-0.02	(-0.09, 0.05)	.579	.020
	PA	31	.624(.220)	27	.599(.224)	20	.589(.222)								
Alpha EC															
	NFB	33	.620(.301)	29	.560(.332)	24	.591(.313)	MPH vs NFB	0.05	(-0.04, 0.14)	.314	-0.03	(-0.12, 0.07)	.537	.011
	MPH	33	.603(.302)	28	.560(.300)	23	.573(.337)	PA vs NFB	0.05	(-0.05, 0.14)	.324	-0.03	(-0.13, 0.06)	.502	.008
	PA	31	.553(.310)	27	.528(.343)	20	.532(.340)								
Beta EC															
	NFB	33	-.340(.155)	29	-.364(.183)	24	-.352(.187)	MPH vs NFB	0.02	(-0.04, 0.07)	.534	<0.01	(-0.06, 0.06)	.914	.529
	MPH	33	-.329(.200)	28	-.348(.205)	23	-.348(.215)	PA vs NFB	0.01	(-0.05, 0.07)	.692	0.01	(-0.05, 0.07)	.684	.963
	PA	31	-.369(.214)	27	-.413(.188)	20	-.396(.201)								
Theta EO[2]															
	NFB	33	.505(.223)	29	.455(.225)	24	.458(.217)	MPH vs NFB	-0.02	(-0.08, 0.04)	.523	-0.01	(-0.07, 0.06)	.800	.608
	MPH	33	.546(.151)	28	.477(.141)	23	.500(.150)	PA vs NFB	0.03	(-0.03, 0.09)	.254	-0.04	(-0.10, 0.03)	.248	.001
	PA	31	.475(.170)	27	.472(.160)	20	.426(.132)								
Alpha EO															
	NFB	33	.291(.251)	29	.246(.278)	24	.258(.248)	MPH vs NFB	0.02	(-0.06, 0.10)	.634	0.05	(-0.03, 0.14)	.217	.231
	MPH	33	.311(.257)	28	.249(.262)	23	.326(.300)	PA vs NFB	0.05	(-0.02, 0.13)	.197	0.01	(-0.07, 0.10)	.764	.148
	PA	31	.204(.232)	27	.210(.283)	20	.202(.254)								
Beta EO															
	NFB	33	-.400(.162)	29	-.443(.183)	24	-.414(.181)	MPH vs NFB	0.04	(-0.02, 0.09)	.211	0.02	(-0.04, 0.08)	.495	.415
	MPH	33	-.377(.200)	28	-.406(.200)	23	-.404(.196)	PA vs NFB	0.02	(-0.03, 0.08)	.416	<0.01	(-0.06, 0.06)	.906	.281
	PA	31	-.457(.220)	27	-.496(.204)	20	-.480(.232)								
Theta task															
	NFB	33	.590(.202)	29	.555(.226)	24	.537(.230)	MPH vs NFB	-0.04	(-0.10, 0.01)	.116	-0.02	(-0.08, 0.03)	.415	.373
	MPH	33	.658(.169)	28	.573(.141)	23	.580(.158)	PA vs NFB	0.02	(-0.03, 0.08)	.373	-0.05	(-0.11, 0.01)	.086	.001

	PA	31	.577(.182)	27	.567(.155)	20	.502(.155)							
Alpha task														
	NFB	33	.216(.229)	29	.191(.262)	24	.173(.211)	MPH vs NFB	-0.04	(-0.10, 0.03)	.256	-0.03	(-0.09, 0.04)	.440	.654
	MPH	33	.280(.220)	28	.186(.170)	23	.222(.228)	PA vs NFB	0.03	(-0.04, 0.09)	.386	-0.03	(-0.10, 0.04)	.396	.012
	PA	31	.157(.254)	27	.153(.287)	20	.110(.221)							
Beta task														
	NFB	33	-.410(.151)	29	-.400(.172)	24	-.391(.155)	MPH vs NFB	-0.02	(-0.07, 0.04)	.563	-0.02	(-0.08, 0.03)	.415	.674
	MPH	33	-.345(.214)	28	-.388(.204)	23	-.383(.206)	PA vs NFB	<-0.01	(-0.06, 0.05)	.948	<0.01	(-0.05, 0.06)	.926	.806
	PA	31	-.440(.231)	27	-.464(.213)	20	-.454(.227)							

Note. EC[1]=eyes closed; EO[2]=eyes open, CI[3]=Confidence Interval.

.

Chapter 6

Learning from feedback in children with ADHD

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Abstract

Objective: The current study examined instrumental learning using consistent versus probabilistic feedback in children with ADHD.

Method: 58 children with ADHD and 58 typically developing (TD) children performed a forced-choice probabilistic learning task using three probability conditions (consistent-, slightly inconsistent-, and inconsistent feedback condition). After learning, generalization of learning to new stimulus-pair combinations was assessed.

Results: Children with ADHD performed less accurate during learning, particularly in the consistent and slightly inconsistent condition. These findings are accompanied by a less steep learning rate, at least in the first few trials. In addition, children with ADHD showed poorer generalization of learning.

Conclusion: Results indicate that children with ADHD show initial learning problems, after which they increased their performance in a similar manner as TD children, independent of whether feedback delivery was consistent or probabilistic. This finding is of clinical relevance as children are often faced with probabilistic feedback in real life.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity and impulsivity.[1]

Instrumental learning, or the ability to change behavior in response to positive and negative feedback, is essential for adaptive functioning.[2] Difficulties with instrumental learning may result in a number of problems in daily life functioning, such as the inability to learn to exhibit 'appropriate' behavioral responses (e.g., withhold impulses, await turns) and inability to act according to social rules, behaviors that are associated with ADHD.[3]

Neurobiological models of ADHD suggest a deficiency in instrumental (or reinforcement) learning due to altered levels and/or activity of striatal dopamine.[4-7] Although, these models differ in level of explanation,[8] they agree on the prediction that children with ADHD show poor reinforcement learning compared to controls, particularly when reinforcement is not delivered consistently and frequently.[4-7] However, experimental studies that manipulated the consistency of reinforcement delivery to investigate this prediction for individuals with ADHD showed inconsistent results.[4,9-11]

Two studies focused on instrumental learning using consistent performance feedback in ADHD compared to typically developing (TD) children. In a study of Luman et al.,[9] children were required to match four stimuli with two responses using consistent performance feedback under four reward conditions that differed in reward frequency and magnitude. In a study of Groen et al.,[12] children were presented with two stimulus pairs. One stimulus pair was coupled with consistent performance feedback while the other stimulus pair was coupled with feedback that was independent of performance. In both studies, children were instructed to win as many points as possible. The two studies found comparable results demonstrating that children with ADHD displayed similar learning rates compared to TD children when learning was required from consistent feedback that was dependent on performance. However, despite similar learning rates, in both studies, children with ADHD stayed behind typical controls in terms of overall performance levels.

In many daily life situations, a child is assumed to adapt behavior by learning from inconsistent or probabilistic feedback.[13,14] Learning from probabilistic feedback is considered more difficult compared to learning from consistent performance feedback.[15] Studies that compared performance on probabilistic learning between ADHD and controls found mixed results.[4,10,11] Frank and colleagues[4] compared a group of adults with ADHD and controls on a probabilistic reinforcement learning task using three stimulus pairs (Chinese characters) with the

following probability conditions: 80-20%, 70-30%, and 60-40%. Results showed that participants with ADHD showed impaired reinforcement learning, as reflected in reduced performance on the task.[4] However, that study did not take learning rate into account. In a study by Luman et al.,[11] four stimuli (simple objects) had to be mapped onto two responses using either consistent performance feedback or probabilistic feedback (probability condition of 88-12%). They found that children with ADHD were as accurate as TD children and showed similar learning rates. Hauser et al.[10] examined learning behavior in a probabilistic reversal learning task in children with ADHD and controls. In this task, children were presented with one stimulus pair using a probability condition of 80-20%. Reinforcement probabilities were reversed after six to ten correct responses. Children with ADHD earned less money during the task compared to controls, indicating less efficient learning, although this difference just escaped conventional levels significance. In addition, Hauser et al.[10] found learning rates to be intact. The finding of intact learning rates in ADHD in studies using consistent performance feedback[9,12] and studies using a relatively simple task with a low number of stimuli,[10,11] suggest that individuals with ADHD may suffer specifically from instrumental learning problems only when feedback is probabilistic and the task requires considerable effort.[4]

The aim of our study was to test whether children with ADHD are impaired in instrumental learning, particularly when feedback is probabilistic.[4-7] In the current study, we used an adapted, child-friendly version of the probabilistic learning task developed by Frank et al.,[13] in a large and well defined group of children with ADHD. We improved upon previous studies[4,11] in several respects. First, we examined instrumental learning performance in children using three probability conditions of 85-15% and 70-30% as compared to consistent performance feedback. Furthermore, instead of evaluating learning rate by analyzing bins of trials,[4,11] we performed a trial-by-trial analysis to improve the sensitivity in detecting differences between groups in learning from divergent feedback contingencies over the course of the task. We predicted that children with ADHD, compared to their age-matched peers, would show more difficulty in instrumental learning, especially in the probabilistic feedback learning conditions.[16] In addition, after learning, we examined the generalization of learning to a new context. We predicted that children with ADHD would reveal poorer generalization of learning compared to their peers.[7]

Methods

Participants and selection procedure

Participants were 58 children with ADHD and 58 typically developing (TD) children, aged 7-13

years. Because previous studies showed developmental improvements in feedback-based learning between ages 8 and 13[14,17] children from the two groups were closely matched on age (within 6 months). All children were required to have IQ scores > 80 as estimated by four subtests of the Wechsler Intelligence Scale of Children-III (WISC-III): Vocabulary, Arithmetic, Block Design, and Picture Arrangement.[18] In addition, all children were free of neurological impairments. Children with ADHD were recruited from fifteen psychiatric outpatient clinics in the west of the Netherlands. Inclusion criteria for the ADHD group were (1) a primary diagnosis of ADHD as established by the clinician using DSM-IV-TR criteria, (2) elevated parent and teacher ratings on the Disruptive Behavior Disorders Rating Scale (DBDRS)[19] with at least one of the scores on the Inattention or Hyperactivity/Impulsivity scale above the 90th percentile for one informant, and above the 70th percentile for the other informant, (3) children being free of stimulant medication for at least one month prior to inclusion in the study. No restrictions were set on other comorbidities. Comorbid disorders were diagnosed according to DSM-IV-TR and retrieved from the medical records. Comorbid disorders in the ADHD group included learning disorders (*n*=5), autism spectrum disorders (*n*=6), anxiety disorders (*n*=2) and mood disorder (*n*=1).

TD children were recruited from primary schools, after school programs and sport clubs. TD children were required to obtain parent and teacher ratings <70th percentile on both scales of the DBD to rule out the presence of significant ADHD symptoms. Table 1 gives an overview of the group characteristics.

Table 1. Group characteristics

	ADHD[1] (*n*=58)	TD Children (*n*=58)	GROUP *F*	*p*
Age, *M(SD)*	9.7 (1.3)	9.9 (1.2)	0.44	ns
Estimated FSIQ, *M(SD)*	99.3 (12.4)	108.0 (11.1)	15.79	<.001
Gender, % male	67	67		
DBDRS Parent				
Inattention, *M(SD)*	16.0 (5.3)	3.3 (3.0)	249.69	<.001
Hyperactivity/Impulsivity, *M(SD)*	13.8 (5.6)	2.8 (2.6)	181.12	<.001
DBDRS Teachers				
Inattention, *M(SD)*	16.1 (5.3)	2.1 (3.6)	276.24	<.001
Hyperactivity/Impulsivity, *M(SD)*	13.1 (8.3)	1.6 (2.9)	99.48	<.001

Note. ADHD=Attention Deficit Hyperactivity Disorder, DBDRS=Disruptive Behavior Disorder rating scale, M=Mean, SD=Standard Deviation.

Measures

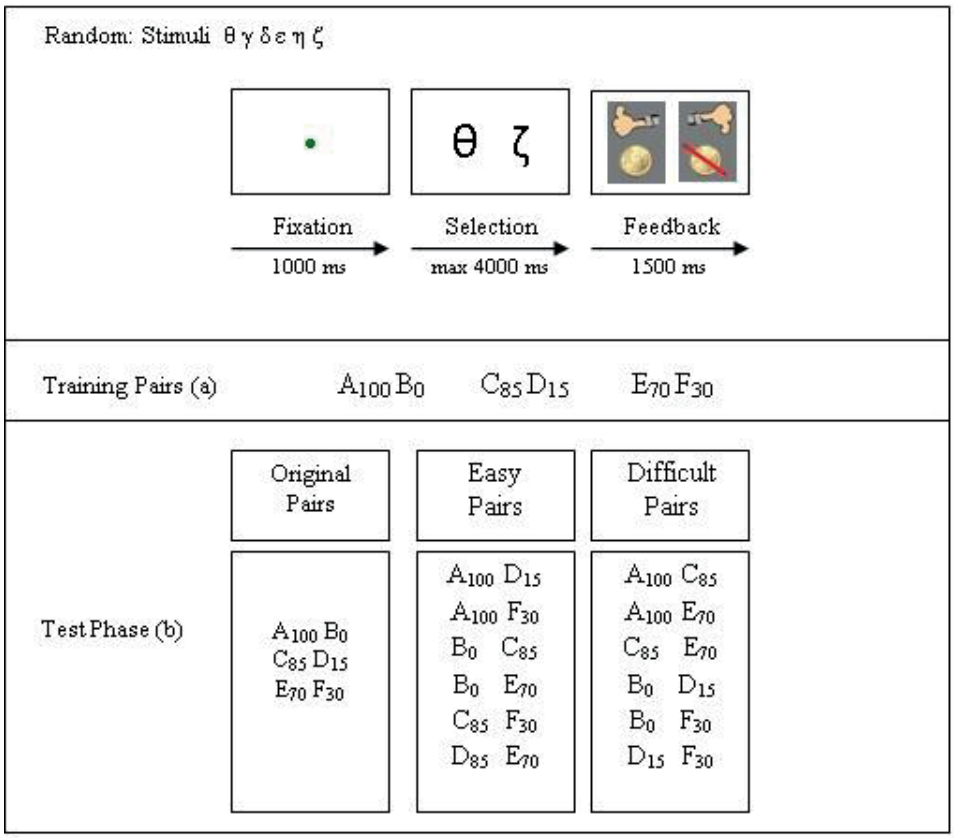
Probabilistic Learning Task. We used a child-friendly version of the extensively validated Probabilistic Learning Test (PLT)[13] to measure feedback learning, which has successfully been used in typical developing children.20 The PLT consisted of a learning phase and a test phase. In the learning phase, children were presented two stimuli in each trial and were instructed to select the stimulus with the greatest probability of positive feedback (Figure 1a). Three fixed pairs (AB, CD and EF), were presented in a random order and children had to learn to choose the stimulus that was associated with positive feedback. Stimuli were represented by randomly chosen characters from the Greek alphabet. Feedback was consistent in the AB pair (A: 100% positive feedback; B: 100% negative feedback) and feedback was slightly inconsistent in the CD pair (C: 85% positive and 15% negative feedback; D: 15% positive and 85% negative feedback) and inconsistent in the EF pair (E: 70% positive and 30% negative feedback; F: 30% positive and 70% negative feedback). Consequently, A, C and E are net positive stimuli and B, D and F are net negative stimuli, and it is increasingly difficult to learn that A, C and E are associated with positive feedback more frequently than B, D, and F. Positive feedback consisted of a 'thumbs up' symbol and a €0.20 gain when the response was correct, and negative feedback consisted of a 'thumbs down' symbol with a €0.20 loss when the response was incorrect. All children were aware that they would not receive any of the gained money after they completed the task, however, they were provided with a small present after finishing the task. Each stimulus pair was presented for 1000ms, followed by a response window of 4000ms maximum. The feedback screen appeared for 1500ms. When no response was given within 4000ms, a 'too late' message appeared on the screen for 1500ms. The learning phase consisted of learning blocks of 60 trials each (20 trials per feedback condition) with a maximum of five blocks. Children that reached above chance level performance in any given learning block (AB, CD and EF pair ≥ 70%, 65% and 60%, respectively) entered the test phase.

In the test phase, no feedback was provided, and children had to select the stimulus most frequently associated with positive feedback in the learning phase from all possible pair configurations of stimuli. The test phase consisted of both easy and difficult pairs. Easy pairs (AD, AF, BC, BE, CF, DE in 60 trials) consisted of one stimulus that was most frequently associated with positive feedback (and thus selected) in the training phase, and one stimulus that most frequently associated to negative feedback (and thus rejected) in the training phase. The difficult pairs (AC, AE, CE, BD, BF, DF in 60 trials) consisted of stimuli that were either both most frequently associated with positive feedback (and thus selected) or both most frequently

associated to negative feedback (and thus rejected) in the training phase. During the test phase eight blocks were presented, with each block containing all 15 possible stimulus pairs presented in random order (each pair was presented 8 times). Task duration ranged between 16.50 and 42.50 minutes.

Dependent variables in the learning phase were (1) the number of learning blocks required to reach the entry criterion for the test phase and (2) learning in the first learning block across trials (1-19) and feedback conditions (consistent-, slightly inconsistent and inconsistent). We removed the first trial of each stimulus pair (guess trials, resulting in 19 trials per feedback condition) and excluded trials with reaction times < 200 ms (anticipatory responses; 0.68%) and trials without a response (omissions; 0.36%). We only examined the first learning block as we were interested in initial learning. Dependent variables in the test phase were the overall percentage correct, percentage correct of original-, easy-, and difficult pairs (Figure 1b). In the test phase, trials with reaction times < 200 ms (0.47%) were excluded from analysis and omissions (0.79%) were interpreted as incorrect responses.

Figure 1 a&b



Note. Probabilistic learning task. **(a)** In the learning phase, children were presented with two stimuli and instructed to select the stimuli with the highest probability to receive positive feedback. During the learning phase stimulus pairs were presented one by one and children had to choose one of both stimuli by pressing '1' or '0' on the keyboard. Positive and negative feedback was provided as shown in parentheses for each stimulus pair. In stimulus pair AB, A always led to positive feedback whereas B always resulted in negative feedback. In stimulus pair CD, selecting C led to positive feedback in 85% of the trials, whereas selecting D led to positive feedback in only 15% of the trials. In stimulus pair EF, stimulus E was followed by positive feedback in 70% of the trials, whereas F was followed by positive feedback in only 30% of the trials. **(b)** In the test phase, novel stimulus pairs were presented to evaluate what was learned in the learning phase. Stimulus pairs were grouped into three categories (original-, easy-, and difficult pairs) according discriminability of the reinforcement values for the two stimuli in a pair during the learning phase (see main text). The difference between the reinforcement values in the learning phase for the easy pairs ranged between 55%-85%, while for the difficult pairs, the difference were smaller ranging between 15%-30%.

Procedure

The PLT was part of a larger assessment battery of a treatment trial for ADHD (Ref. No. NCT01363544, https://clinicaltrials.gov/show/NCT01363544). The study was approved by the national medical ethics committee (NL 31641.029.10 CCMO). All children verbally agreed to participate and written informed consent was obtained before participation from all parents and children aged 11 years and older. Children received a small gift to thank them for participating in the study.

Statistical Analysis

Analyses were performed with Statistical Package for the Social Sciences version 18.21 Group comparability in terms of background characteristics was analyzed using a chi-square test (χ^2) or analyses of variance (ANOVA).

Learning Phase. To investigate group differences (ADHD versus TD children) in learning performance, we compared (1) the number of learning blocks required to reach the entry criterion for the test phase using ANOVA and (2) accuracy and learning rate over trials (1-19) and conditions (consistent feedback condition = AB stimulus pair, slightly inconsistent feedback condition = CD stimulus pair, and inconsistent feedback condition = EF stimulus pair), using generalized estimating equations (GEE) with an identity link function and an autoregressive (AR(1)) working correlation matrix. Main effects were group, trial, and condition. Possible significant interactions of group by trial were followed by post-hoc analysis in which the first block (19 trials) was split up in two halves (the first ten trials versus the last nine trials); significant interactions of group by condition, were followed by post-hoc analyses including pairwise comparisons to examine possible group differences within each feedback condition and to examine possible differences between feedback conditions within groups (ADHD and TD children group).

Test Phase. If children did not reach the performance criterion to proceed to the test phase for all three stimulus pairs after a maximum of five learning blocks (300 trials), their test phase results were omitted from the statistical analysis. We evaluated group differences in the ability to reproduce what had been learned during the learning phase, using data derived from the test phase. In the test phase we compared groups on the overall percentage correct for the original pairs (AB, CD and EF) using ANCOVA. Results on new (i.e. easy- and difficult) pairs (Figure 1b) were examined using a repeated measures (RM) ANCOVA with pairs (easy- and difficult pairs) as within-subject factor and group (ADHD and TD) as between-subject factor. Because we assumed that the overall percentage correct in the test phase would be influenced by the learning phase,

percentage correct for the last block of the learning phase was used as a covariate in the analysis to control for possible group differences in accuracy during the learning phase.

Results

Group characteristics

Group characteristics are summarized in Table 1. Children with ADHD had lower IQ scores than TD children, but did not differ in age or gender. To investigate whether IQ influenced the results sensitivity analysis were performed (see below). As a result of the selection procedure, children with ADHD obtained higher scores on all the ADHD symptom measures (Table 1).

Learning Phase

To reach the entry criterion for the test phase, children with ADHD needed on average a half learning block extra compared to TD children, $F(1, 114) = 4.71$, $p = 0.032$ (see Table 2).

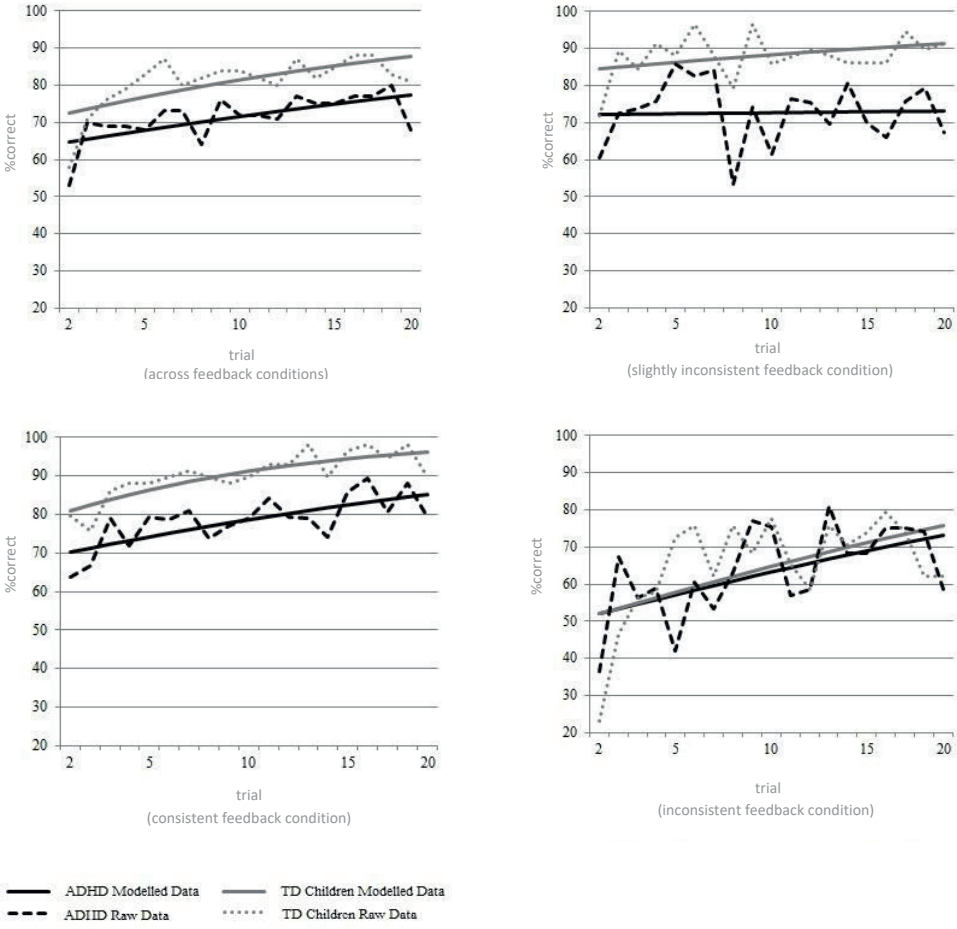
Results for accuracy over trials in the first block for the two groups are shown in Figure 2 and Table 2. A significant main effect of group was found: Across trials and conditions children with ADHD achieved a lower percentage correct than TD children, Wald $\chi2$ (1) = 19.54, $p < 0.001$. Accuracy increased over the course of the first block as indicated by a significant main effect of trial, Wald $\chi2$ (1) = 41.93, $p < 0.001$. Further, accuracy differed between feedback conditions in the first block, Wald $\chi2$ (2) = 103.68, $p < 0.001$. Overall, as expected, children achieved a higher percentage correct in the consistent feedback condition compared to slightly inconsistent feedback condition, Wald $\chi2$ (1) = 7.69, $p = 0.006$, and the inconsistent feedback condition, Wald $\chi2$ (1) = 91.69, $p < 0.001$. Accuracy in the slightly inconsistent feedback condition was higher compared to the inconsistent feedback condition, Wald $\chi2$ (1) = 56.10, $p < 0.001$.

The interaction between group and trial was significant, Wald $\chi2$ (1) = 3.97, $p = 0.046$, indicating that across conditions the learning curve differed between groups (Figure 2a, upper left panel). Post hoc tests showed that children with ADHD had more difficulty learning from the feedback in the first half of the block compared to TD children as indicated by a significant interaction between group and the first 10 trials, Wald $\chi2$ (1) = 4.79, $p = 0.029$. No significant interaction was found between group and the last 9 trials, Wald $\chi2$ (1) = 0.013, $p = 0.908$.

We found a significant interaction between group and feedback condition, Wald $\chi2$ (2) = 20.40, $p < 0.001$. Pairwise comparisons between groups showed that children with ADHD achieved a lower percentage correct in the consistent feedback condition, $F(1,114) = 15.04$, $p < 0.001$, and slightly inconsistent feedback condition, $F(1,114) = 21.25$, $p < 0.001$, than TD children.

No group differences were observed in the inconsistent feedback condition, $F(1,114) = 0.27$, $p = 0.604$). The three-way interaction of group by trial by condition was not significant, Wald $\chi 2$ (2) = 1.89, $p = 0.388$.

Figure 2.



Note. Learning curves in the first learning block for children with ADHD and TD children collapsed over feedback conditions (panel a) and for the consistent condition (panel b), slightly inconsistent condition (panel c), and inconsistent feedback condition (panel d). Raw data represents the actual data while modelled data shows data as modelled by the generalized estimating equations (GEE) analyses that were used to compare the learning curves between groups over trials and conditions. The upper left graph represents the learning curves of children with ADHD and TD children across conditions, showing a significant interaction between group and trial which seems to driven by the shallower learning curve of children with ADHD at the beginning of the learning phase.

We tested whether the results found in the learning phase may be explained by lower IQ scores observed in the ADHD group (see Table 1). Therefore, we conducted a sensitivity analysis adding IQ as a covariate. Sensitivity analyses including IQ as covariate did not change our main findings.

Test Phase

Data of seven children (ADHD; n=5; TD; n=2) were not included in these analyses, because these children did not reach the performance criterion, leaving a total of 53 children with ADHD and 56 TD children for analysis. Attrition analyses showed no differences in group characteristics between the initial sample (ADHD; n=58; TD; n=58) and the sample that reached the performance criterion of the learning phase (ADHD; n=53 ; TD; n=56) (p values > .762). Since we assumed that the outcome measures in the test phase would be influenced by accuracy in the learning phase, percentage correct for the last block of the learning phase was used as a covariate in the analysis to control for individual possible group differences in accuracy during the learning phase. Compared to TD children, children with ADHD achieved a lower overall percentage correct (see Table 3) in the test phase when controlling for performance in the learning phase, $F(1,106)=5.72$, $p=.018$, $\eta_p^2=0.05$. Further, children with ADHD obtained lower percentages correct on the original pairs (AB, CD, and EF), $F(1,106)=4.94$, $p=.028$, $\eta_p^2=0.05$. Groups also differed on the new pairs, $F(1,106)=5.00$, $p=.027$, $\eta_p^2=0.05$, indicating that children with ADHD performed less accurately compared to TD children, but there was no significant interaction between easy- and difficult pairs and group, $F(1,106)=0.33$, $p=.565$, $\eta_p^2<0.01$.

Table 3. Accuracy in Test Phase for children with ADHD and TD children.

Measure	ADHD (n=53)		TD Children (n=56)	
	M	*SD*	*M*	*SD*
Overall % correct	72.3	10.6	77.3	8.5
Original % correct	80.8	15.4	88.2	12.1
Easy % correct	80.8	14.7	87.1	12.2
Difficult % correct	59.3	13.3	62.1	12.3

Note. Stimulus pairs were grouped into three categories (original-, easy-, and difficult pairs) according discriminability of the reinforcement values for the two stimuli in a pair during the learning phase. SD = Standard deviation

Discussion

In the present study, we investigated whether children with ADHD showed difficulties in instrumental learning compared to age-matched TD children on a task with relatively difficult stimuli. We expected the largest group differences in probabilistic feedback conditions. Our findings indicated that in the learning phase, children with ADHD needed more learning blocks to achieve the performance criterion (reaching above chance level performance) than TD controls. Analyses of learning performance in the first learning block revealed a less steep learning rate in the first few trials for children with ADHD compared to TD children, driving a lower performance in the ADHD group within this block. In addition, children with ADHD achieved significantly lower accuracy levels in the consistent and slightly inconsistent feedback condition, but not in the inconsistent feedback condition. Finally, in the test phase, children with ADHD performed less accurate than TD children in generalizing what they had learned to novel stimulus-pair combinations. Findings were unrelated to estimated IQ scores.

The increase in accuracy over the course of the task for all feedback conditions (main effect of trial) validated the assumption that learning took place. As expected, children reached highest levels of accuracy in the consistent feedback condition, followed by the slightly inconsistent feedback condition and the inconsistent feedback condition, respectively. These results confirmed that learning from probabilistic feedback is more difficult compared to learning from consistent feedback.[11,15] Overall, like adults with ADHD,4 children with ADHD needed more learning blocks to achieve the performance criterion to enter the test phase compared to TD children, supporting the hypothesis of impairments in instrumental learning in ADHD. To provide more insight in group differences in terms of learning curves within and between feedback conditions, we analyzed trial-by-trail learning performance in the first learning block.

In the first learning block, learning curves regardless of feedback condition differed between groups regardless of feedback condition. Post-hoc analyses showed that a lower response accuracy and a less steep learning rate in children with ADHD compared to TD children were driven by the first few (seven) trials (first task half). Within an instrumental learning task, the first few trials are essential to map the stimulus-response relation. Visual inspection of Figure 2a, displaying the learning curves across the feedback conditions, indicates a similar learning rate in the first few trials after the guess trial. However, after trial three, differences in performance appeared as TD children showed a steeper learning rate compared to children with ADHD. In the subsequent trials, performance of children with ADHD stayed behind that of TD children, as learning curves in both groups increased in a similar trend. Note that previous studies only

detected lower accuracy levels in children with ADHD compared to TD children and found no group differences in learning rates.[9-12] We speculate that impaired learning rates in ADHD may only be present when memory load is high, using relatively difficult stimuli (Greek letters in our study as compared to simple concrete visual stimuli in other studies),[9,12] and when learning exceeds two stimulus pairs (three stimulus pairs in our study as compared to either one or two stimulus pairs in previous work).[10-12] Under these conditions, one might speculate that impaired fundamental processes such as attention and working memory, known to be disturbed in ADHD, possibly contribute to the explanation of impaired performance on the initial learning trials in children ADHD.[14]

In the current study, children with ADHD achieved a lower percentage correct when learning from consistent and slightly inconsistent feedback compared to TD children. Visual inspection of Figure 2b and 2c, displaying the learning curves of the consistent and slightly inconsistent feedback condition, shows that children with ADHD start at a lower percentage correct after the guess trial. In subsequent trials, both groups showed parallel learning curves and children with ADHD did not catch up with TD children. This finding supports our hypothesis of children with ADHD being impaired in instrumental learning. However, learning performance in the inconsistent feedback condition (probability of reinforcement 70-30%) did not differ between groups. The lack of a group difference in the inconsistent condition is in line with Frank et al.,[4] who found no group differences in learning from inconsistent feedback (probability of reinforcement 60-40%) in an adult sample. Possibly, this result is caused by a floor effect in the initial learning trials of the inconsistent feedback condition (which cannot be lower than chance level). Figure 2 shows that although children with ADHD show a blunted learning curve compared to the TD group in the first half of the block, they show complete catch up thereafter. We speculate that because of the inconsistent feedback in this condition, it took children in both groups long to choose the stimulus with the greatest probability of positive feedback.

Generalization is an important skill to successfully adapt behavior.[22] In the present study, we examined generalization of learning in the test phase. Our findings in the test phase are in accordance with predictions of neurobiological models of ADHD[4,7] suggesting a deficiency in reinforcement learning. Indeed, children with ADHD obtained lower percentages correct when generalizing what they learned to novel stimulus-pair combinations, independent of whether stimulus pairs were easy or difficult, supporting the idea of a deficiency in generalization of learning in children with ADHD. The group differences in performance during the test phase were significant, however effect sizes were small.

An interesting alternative explanation of the lower accuracy of the ADHD group in the learning phase, is that individuals with ADHD may show a greater 'exploration rate' (or greater choice stochasticity) rather than a reduced steepness in learning curve.[10,23] Using computational modelling, Hauser et al.[10,23] but also alternative studies by Williams & Dayan[24] and Williams & Taylor,[25] showed that reinforcement learning performance in ADHD is characterized by more exploratory behavior meaning that individuals with ADHD would examine the alternative option more frequently than controls. Although exploratory behavior is necessary to detect changes in reinforcement delivery, according to the computational model of Hauser et al.,[10] individuals with ADHD show too much exploratory behavior causing them to underachieve compared to healthy controls. To disentangle reduced learning from increased choice stochasticity, future studies should incorporate computational modelling to examine mechanisms behind the increased exploratory behavior in ADHD, which was beyond the scope of the current study.

The present study carries some limitations that should be addressed. First, children with ADHD had lower IQ scores compared to TD children that may have influenced learning performance. However, we found performance in both groups independent of IQ, making it unlikely that the observed group differences might be related to the differences in IQ. Second, in the learning phase we used a performance criterion to enter the test phase. However, performance of children with ADHD (M = 85.7% SD = 7.6%) was worse compared to TD children (M = 89.3% SD = 5.4%) in the last block of the learning phase: $F(1, 107) = 8.29$, $p = 0.005$. Therefore, one may argue that not every child had the chance to get equally familiar with the stimulus-response couplings before entering the test phase. To control for this effect the analyses on the data of the test phase were adjusted for performance on the last block of the learning phase. Third, children in the current study were aware that they would not receive any of the gained money. Instead they would only receive a small gift after they completed the task. In children with ADHD, this might have affected their motivation to learn[5,6] and may have drawn their attention away from making an effort. However, the modest feedback contributes to the ecological validity of the paradigm.

Summary and Clinical implications

Results in the current study indicate that children with ADHD are capable of learning from feedback, although they need more trials to reach the performance criterion compared to TD children. Analyses of the first learning block showed less steep learning rates in children with ADHD compared to TD children, post-hoc analyses revealed this result is driven by impaired performance on initial trials. Although children with ADHD stayed behind controls after these

'start up problems', they seem capable of learning from feedback like TD children, or even show catch-up and reach the level of TD children in the inconsistent feedback condition. This confirms that children with ADHD are able to adjust their behavior, in order to meet task demands.[26] In addition, we found poorer generalization of what was learned in children with ADHD compared to TD children, which confirms the idea of an overall impairment in reinforcement learning in children with ADHD. This result is in accordance with predictions of neurobiological models of reinforcement learning in ADHD.[4-7] However, the prediction of specific impairments in learning when feedback is probabilistic was not supported. More specifically, our results did not demonstrate a difference between groups when feedback was highly inconsistent. According to our findings, children with ADHD may benefit, like TD children, from probabilistic feedback. Finally, children with ADHD show difficulty with the generalization of learned knowledge to novel situations. Although effects were small, the latter finding might add to an explanation of impaired school performance in children with ADHD. However, more research on generalization of learning is necessary to offer practical recommendations to enhance learning performance in children with ADHD.

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Chapter 7

Summary and Discussion

Summary

The first aim of this thesis was to investigate whether children with ADHD improve in behaviour and neurocognitive functioning from neurofeedback as standalone treatment compared with stimulant medication use and with physical activity used as a semi-active control condition. A randomized controlled multicentre three-way parallel group design was used to evaluate direct and long-term effects on behaviour and neurocognitive functioning. The second aim of this thesis was to explore possible working mechanisms underlying the effects of neurofeedback by investigating possible long-term changes in brain electroencephalogram (EEG) six months after children had received neurofeedback, and by examining feedback learning in children with ADHD. The description of the investigated sample of children with ADHD, the interventions and the main results from the research are summarised below. An overview of the main results is provided in Table 1. The discussion addresses the findings within the scientific context and possible future implications for research and clinical practice.

Sample description

Children with ADHD. In chapter 2-5, we described a sample of children with ADHD who were treated within one of the three treatment arms of the current study. Eligible participants were Dutch speaking children, 7-13 years with a primary clinical DSM-IV-TR diagnosis of ADHD,[1] an estimated IQ>80, and no neurological disorders. The diagnosis ADHD was confirmed by parent and teacher reports (Disruptive Behavior Disorders Ratings Scale (DBDRS)2). Furthermore, children had to be free of stimulants for at least one month prior to the intervention. At pre-, post-intervention, and at six-month naturalistic follow-up, children were evaluated on behaviour measures rated by both parents and teachers, neurocognitive, and neurophysiological measures.

Typically developing (TD) children. In chapter 6, where we explored feedback learning in children with ADHD, we also report on typically developing (TD) children. TD children, 7-13 years with an estimated IQ<80 and free of any psychiatric disorder, were recruited from primary schools, after school programs and sport clubs. TD children were required to obtain parent and teacher ratings <70th percentile on both scales of the DBDRS to rule out the presence of significant ADHD symptoms.

Interventions

All three interventions took place over a period of 10-12 weeks. The neurofeedback and physical activity interventions consisted of three individual training sessions a week, with each session lasting 45 minutes including 20 minutes of effective training.

Neurofeedback. Theta/beta training was applied with the aim to inhibit theta (4-8Hz) and reinforce beta (13-20Hz) activity at Cz. Theta/beta index was represented to the participant by simple graphics on a screen. Successful reduction of the theta/beta index as averaged over one trial relative to session baseline, was rewarded with the appearance of a sun and granted with credits. To promote generalization of the learned strategies into daily life, transfer trials were used. Transfer trials were presented without immediate visual feedback and were included from session 11 (25%) and session 21 (50%) onwards. To further transfer learned behaviors, participants were instructed to retrieve their neurofeedback experiences by watching printed graphics of the training during school and homework.

Medication. A four-week double-blind randomized placebo-controlled titration procedure was used to determine the optimal individual dose of short-acting methylphenidate (MPH).3 The titration phase was preceded by a baseline week to determine ADHD symptoms without MPH, and was followed by a lead-in week in which on three consecutive days, twice-daily (at breakfast and lunch time), doses of (1) 5mg, (2) 10mg, and (3) 15mg (<25kg body weight) or 20mg MPH (>25kg body weight) were used to assess possible adverse effects. During the four week titration phase, children received in pseudo-random order (1) 5mg, (2) 10 mg, (3) 15mg or 20 mg MPH or (4) placebo for one week, twice daily. During the titration phase, children, parents and teacher as well as the researchers were blind with regard to the prescribed dose (placebo, 5, 10 or 15/20 mg). At the end of each week, parents and teacher were asked to evaluate inattention and hyperactivity/impulsivity symptoms on the DBDRS, and adverse effects on the MTA Side Effect Rating Scale.[4] Children were classified by a standardized procedure[5] as responders when their ADHD symptoms significantly decreased compared to placebo. The standardized procedure[5] classified children as non-responders when they did not show any decrease in inattention and hyperactivity/impulsivity symptoms across MPH doses and placebo. Non-responders were treated with 5mg MPH twice daily. When children were found to respond equally well across different MPH doses, the lowest MPH dose was prescribed. The child's psychiatrist prescribed the optimal dose for the remaining intervention period.

Physical activity (semi-active control condition). Maximum heart rate (HRmax) was determined before the start of the first training session using a standard maximum heart rate test.

Each training session started with 5 minutes of warming up, followed by five 2-minute moderate intensity exercises at a level of 70-80% of HRmax. After a 5-minute break, five 2-minute vigorous intensity exercises of 80-100% of HRmax were performed. Each training finished with a 5-minute cool down. Time and heart rate were monitored and registered using a POLAR FT4 watch (Polar Electro Oy, Kempele, Finland).

Chapter 2: Behavioural effects of neurofeedback in ADHD at post-intervention

In **chapter 2**, we investigated the effects of theta/beta neurofeedback (n=39), an optimal dose of methylphenidate (n=36), and physical activity (n=37) as a semi-active control group, on behavioural measures of inattention, hyperactivity/impulsivity and psychosocial functioning in 6children with ADHD, as rated by both parents and teachers. In addition, we explored specific treatment effects of neurofeedback by assessing treatment expectations of both parent and teachers and by evaluating quality of sleep.

Results of intention-to-treat analyses showed that parents reported an improvement in psychosocial functioning and hyperactivity/impulsivity for children in all three groups immediately post intervention (η_p^2= 0.21-0.22, p<.001). On the measure of inattention, parents reported greater improvements for children who received methylphenidate compared to both neurofeedback and PA (η_p^2= 0.13, p<.001). Teachers reported a decrease in ADHD symptoms on all measures for children in the methylphenidate group, but not for the neurofeedback or physical activity groups (range of η_p^2= 0.14-0.29, p<.001). In addition, there was a relationship between higher parental expectations and greater parent-reported improvements on inattention for children in the neurofeedback group, indicating possible non-specific effects.

In conclusion, this study found superior effects among children who were randomized to the optimally titrated methylphenidate group compared to children in the neurofeedback and physical activity group in terms of a decrease in symptoms of ADHD at post-intervention.

Chapter 3: Neurocognitive effects of neurofeedback in ADHD, at post-intervention

Using the randomised controlled trial study described above, in **chapter 3**, we examined the effects of neurofeedback (n=39) compared to methylphenidate (n=36) and physical activity (n=37) on attention, inhibition and working memory, neurocognitive functions that play a key role in explanatory models of the disorder 7. These aspects of neurocognitive functioning were assessed using parameters derived from the auditory oddball task, stop-signal task and visual spatial working memory task.

Intention-to-treat analyses showed improved attention as well as inhibition for children who were randomized in the methylphenidate group compared to the children in the neurofeedback and semi-active control group (range of η_p^2= 0.13-0.21, p<.001). Working memory improved over time, irrespective of the received intervention.

In conclusion, this study showed superior effects of children who were randomized to the methylphenidate group compared to children in the neurofeedback and physical activity group in improving neurocognitive functioning. The findings thus do not support the use of theta/beta training as a stand-alone treatment for children with ADHD.

Chapter 4: Behavioural and neurocognitive effects of neurofeedback in ADHD, at follow-up

An important issue when assessing the effectiveness of neurofeedback is whether treatment effects persist after the intervention has ended,[6] and/or whether possible delayed effects occur which could be measured at follow-up. In **chapter 4**, at six month follow-up, we investigated long-term effects of neurofeedback (n=33), methylphenidate (n=28), and physical activity (n=31), on both the parent and teacher rated behavioral outcome measures and the neurocognitive outcome measures in children with ADHD. All measures reported in **chapters 2 and 3** were repeated six months after the intervention ended.

Longitudinal hierarchical multilevel model analyses revealed that at follow-up superior effects of methylphenidate, found at post-intervention, became smaller or non-significant compared to children who received neurofeedback. Further, analyses showed no significant group differences for parent reports on behavioral and neurocognitive measures (p = .058−.997), except for improved inhibition in the methylphenidate group compared to children in the neurofeedback group (p = .040) and faster response speed in children in the neurofeedback group compared to children in the physical activity group (p = .012) as measured with the stop-signal task. These effects, however, disappeared after controlling for medication use at follow-up. Interestingly, teacher reports showed larger improvements (less inattention and hyperactivity/impulsivity) at follow-up for children in the neurofeedback group than for children in the physical acivity group (p = .004−.010), even after controlling for medication use (p = .013−.036). However, some children had different teachers at follow-up than at pre- and post-intervention. Therefore, this finding should be interpreted with caution.

All in all, findings suggest that the effect of stimulant medication remained more or less stable over time, while the neurofeedback and semi-active control groups revealed similar improvements over time. Overall, these findings suggest no evidence for long-term effects of neurofeedback.

Chapter 5: EEG power spectra effects of neurofeedback in ADHD, at follow-up

Much debate has focused on whether the effects induced by neurofeedback are specifically mediated by altered brain function.[8-11] In **chapter 5**, we explored whether neurofeedback induced specific neurophysiological effects compared to methylphenidate and physical activity in children with ADHD at six-month follow-up. EEG power spectra measures of theta, alpha and beta activity, during resting and task conditions, were recorded at pre- and post-intervention and again six months later for 24 children in the neurofeedback group, 23 children in the medication group and 20 children in the PA group.

Results revealed that although for some conditions and power bands, significant time by group interactions emerged, none of the group comparisons on the post-intervention and follow-up assessment data were significant. Over time, EEG power spectra of all three interventions came closer together without one intervention being superior to another. These results are in accordance with the long-term behavioural parent reports and neurocognitive functioning described in **chapter 4**, indicating no difference between all three groups at follow-up. Taken together, our findings suggest no evidence for the specificity of neurofeedback.

Chapter 6: Learning from feedback in children with ADHD

Children with ADHD are thought to have difficulties with instrumental learning, especially when feedback is inconsistent or probabilistic.[12,13] In **chapter 6,** we explored instrumental learning in children with ADHD, particularly when feedback is probabilistic. Further, we evaluated the ability to generalize what was learned to novel situations. Participants were 58 children with ADHD, from the study described above, and 58 typically developing (TD) children. Children were presented with a forced-choice probabilistic learning task, using three probability conditions (consistent, slightly inconsistent or inconsistent feedback). The task had a learning phase, where children received feedback on their choices, followed by a test phase which examined how well they could generalize learning to a new context.

Results revealed that children with ADHD performed less accurately than TD children during the learning phase, particularly in the consistent and slightly inconsistent feedback conditions. We found no difference between groups in the inconsistent feedback condition. Analyses of the first learning block showed the less steep learning rates in children with ADHD were driven by impaired performance on initial learning trials. The ADHD group also showed poorer generalization of learning.

In conclusion, results indicated that children with ADHD showed initial learning problems, after which they increased their performance in a similar manner as TD children, independent of whether feedback delivery was consistent or probabilistic. In addition, we found poorer generalization of what was learned in children with ADHD compared to TD children. Although effects were small, the latter finding might add to an explanation of impaired school performance in children with ADHD. However, more research on generalization of learning is necessary to offer practical recommendations to enhance learning performance in children with ADHD.

Table 1. Summary of methods and main findings in the chapters of this thesis.

Chapter	Participants	Statistical approach	Measures	Main findings
2	112 children with ADHD of whom *n*=39 were randomized to neurofeedback intervention (NFB), *n*=36 to stimulant medication intervention (MPH), and *n*=37 to physical activity intervention (PA)	Repeated measures (RM) analysis of variance (ANOVA) was used to analyze post-intervention effects.	• Parent- and teacher-rated ADHD symptoms on Strength and Difficulty Questionnaire (SDQ) • Parent- and teacher-rated ADHD symptoms on Strengths and Weaknesses of ADHD symptoms and Normal behavior scale (SWAN) both Inattention & Hyperactivity/Impulsivity scale • Parent-rated side effects on Sleep Disturbance Scale (SDSC) • Parent- and teacher-rated treatment expectancies (assessed only at pre-intervention)	• No group differences in improvement in parent-rated behavior on SDQ & SWAN Hyperactivity/Impulsivity scale • MPH showed greater improvement in parent-rated SWAN Inattention compared to both NFB and PA • MPH showed greater improvement in teacher-rated SDQ and both SWAN scales compared to both NFB and PA • Only for NFB, higher parent expectations were predictive of greater improvements on parent-rated SWAN Inattention scale • Quality of sleep (SDSC) did not change over time for any of the intervention groups
3	112 children with ADHD of whom *n*=39 were randomized to NFB intervention, *n*=36 to MPH intervention, and *n*=37 to PA intervention	Repeated measures (RM) analysis of variance (ANOVA) was used to analyze post-intervention effects.	• Auditory oddball task • Stop-signal task • Visual spatial working memory task	• MPH showed greater improvement on neurofeedback attention, reflected by decreased response speed during the auditory oddball task compared to both NFB and PA • MPH showed greater improvement on inhibition, impulsivity and attention, as reflected by faster stop signal reaction times, lower commission and omission error rates during the stop-signal task compared to both NFB and PA • No group differences in improvement in working memory

4	At six-month follow-up, 92 children with ADHD were re-assessed of whom *n*=33 of the NFB intervention, *n*=28 of the MPH intervention, and *n*=31 of the PA intervention	Longitudinal hierarchical multilevel model analyses	• Parent- and teacher-rated ADHD symptoms (SDQ) • Parent- and teacher-rated ADHD symptoms (SWAN both Inattention & Hyperactivity/Impulsivity scale) • Parent-rated side effects (SDSC) • Parent- and teacher-rated treatment expectancies (assessed only at pre-intervention) • Auditory oddball task • Stop-signal task • Visual spatial working memory task	• No group differences on parent-rated behavior • No group differences on neurocognitive measures, except for improved inhibition in MPH compared to NFB and faster response speed in NFB compared to PA during the stop-signal task. However, these effects disappeared after controlling for medication use at follow-up • NFB showed greater improvement on teacher-rated behavior on SWAN Inattention and Hyperactivity/Impulsivity scale compared to PA. However, some children had different teachers at follow-up. Therefore, this finding should be interpreted with caution.
5	At six-month follow-up, 67 children with ADHD were available for EEG analyses of whom *n*=24 of the NFB intervention, *n*=23 of the MPH intervention, and *n*=20 of the PA group	Longitudinal hierarchical multilevel model analyses	• EEG power spectra measures of theta, alpha and beta activity during resting and task conditions	• No group differences during resting and active task conditions between MPH and NFB, and PA and NFB at six-month follow-up

6	58 children with ADHD 58 TD children	Regression analyses with generalized estimating equations (GEE) method	• Probabilistic learning task measuring instrumental learning in three probability conditions; consistent-, slightly inconsistent, & inconsistent feedback condition	• Children with ADHD performed less accurate in the consistent and slightly inconsistent feedback condition • Children with ADHD showed overall less steep learning rate compared to TD children • No group differences in accuracy were found in the inconsistent feedback condition • After learning, children with ADHD performed less accurate compared to TD children

General Discussion

The overall aim of our intervention study was to compare the effects of theta/beta neurofeedback with methylphenidate, using physical activity as a semi-active control group to control for non-specific effects such as parental engagement and personal attention. If neurofeedback could be shown to be as effective in reducing symptoms of ADHD as medication, this would offer an alternative treatment option with less risk of undesirable side effects than seen with stimulant medication. It would have particular clinical significance if beneficial effects of neurofeedback could be shown to persist long-term. The study was carefully designed to provide robust evidence (see Strengths and Limitations section below) and also considered possible working mechanisms underlying the effects of neurofeedback.

The key finding from this study was that neurofeedback was less effective at post-intervention than methylphenidate in reducing symptoms of ADHD, according to both parent and teacher ratings of child behavior and neurocognitive measures. At six-month follow-up, the neurofeedback group had caught up to some extent as there was no longer a significant difference between the neurofeedback and methylphenidate intervention group on measures as rated by parents and neurocognitive outcome measures. These results are in accordance with our findings on EEG effects at follow-up. Interestingly, ratings by teachers at follow-up did show better outcomes for children receiving neurofeedback compared to the semi-active control group undertaking physical activity, although as we discuss below (Possible delayed impact), this finding needs to be treated with caution.

Optimal dosage

Our finding of the superior effects of methylphenidate compared to neurofeedback on behavioural symptoms of ADHD are in line with the results of an RCT by Ogrim and Hestad[9] who also compared the effects of neurofeedback to stimulant medication. Similar to our study, this RCT used a double blind titration procedure to determine an optimal dose of medication. In contrast, Duric et al.[14] and Meisel et al.,[15] found similar reductions in ADHD behaviours for neurofeedback and methylphenidate. However, those studies used weight-adjusted dosing to determine medication dose.[14,15] These results might indicate that the use of disparate medication protocols could explain the discrepant findings. Supporting evidence for the supremacy of the medication procedure used in the current intervention study is found in results of the NIMH Collaborative Multisite Multimodal Treatment Study of Children With Attention-Deficit/Hyperactivity Disorder (MTA). The MTA study indicated that a titration procedure, comparable to the procedure used in our study,

established higher success rates compared to standard community care.[3]

Since the superior effects of stimulant medication appears to depend on identifying the optimal dose for each child, it could be argued that a similar individualized approach to neurofeedback training might make neurofeedback equally effective. However, individualized neurofeedback protocols have not been shown to improve either behavior or neurocognitive functioning.[16,17] The latter study used an individualized (theta/beta) EEG neurofeedback protocol based on visual inspection of the raw EEG and quantitative EEG (QEEG) to determine the EEG neurofeedback training. Individualized EEG neurofeedback was compared to placebo neurofeedback, and the results showed that the EEG neurofeedback was not superior to placebo neurofeedback on the behavioral or neurocognitive outcomes studied.

Treatment expectancy and parental investment

As described in **chapter 2**, at post intervention parent reports indicated similar improvement for two out of three behavioral measures while teachers did not report any decrease in ADHD symptoms in children who received neurofeedback or physical activity. The discrepancy between the effectiveness of the three interventions as reported by parents and teachers might be explained in terms of differences between raters in their investment in the intervention.[18,19] Neurofeedback and the physical activity sessions required direct involvement and commitment from parents, while teachers had a rather passive role. Another possibility is that treatment expectancy of parents and teachers confounded our measures. We measured treatment expectancy in both parents and teachers, and found that only for the neurofeedback group, higher parental expectations were predictive of greater improvements on inattention symptoms. This finding suggests that the parent-reported decrease in inattention problems in the neurofeedback group may at least partly be explained by parental expectations.

Selection of neurofeedback protocols

There is an ongoing debate about the efficacy of various neurofeedback protocols. The current study used the theta/beta training protocol. This protocol is based on findings of increased theta (4-8Hz) and decreased beta (13-20Hz) in ADHD.[20] The rationale for the theta/beta ratio as a clinical biomarker of ADHD has been questioned.[21-23] Arns et al.[24] speculated that neurofeedback does not necessarily focus on adjusting neural dysfunction but rather enables the child to learn compensatory mechanisms. Arns et al.[24] theorized that children could learn to be in an attentive state and thereby strengthen the underlying neural networks. If this were the case, neurofeedback

would be expected to improve behavior unless learning does not take place or people are unable to learn (from feedback). In the present study, we were able to show that learning did take place during neurofeedback sessions,[25] and that children with ADHD are able to learn from feedback **(chapter 6)**. A further hypothesis linked to the 'learning' argument above could be that children with ADHD experience difficulty generalizing what is learned **(chapter 6)**, meaning that they are impaired at retrieving learned knowledge, i.e. an attentive state, in novel situations.

Possible delayed impact

In **chapter 4** naturalistic six-month follow-up data was analyzed, results of parent reports and neurocognitive outcome measures revealed that the previously found superior results for the stimulant medication group immediately post-intervention, became smaller or non-significant at follow-up compared to the neurofeedback group. If we were to speculate that the effects of stimulant medication would remain more or less stable over time at the time of follow-up, then the results obtained for the neurofeedback and the physical activity group could be interpreted as reflecting delayed effects. However, we aimed to control for non-specific effects using the physical activity group as a semi-active control group. Therefore the improvements over time probably reflect non-specific effects, such as developmental effects and/or regression to the mean, unrelated to specific treatment components.

Interestingly, at follow-up, teacher reports showed larger improvements for neurofeedback than for the semi-active condition (although see below under 'Limitations'). This result provides possible evidence for the specificity of improvements with neurofeedback compared to the semi-active control group. Again, a possible explanation might be that the effects of neurofeedback do not emerge immediately after the intervention but rather show a delayed onset. Arns & Kenemans[26] proposed a model in which neurofeedback alters both sleep and ADHD problems in a sub-group of ADHD. They suggest that neurofeedback impacts the sleep spindle circuitry resulting in increased sleep spindle density and normalization of sleep onset insomnia, thereby affecting the noradrenergic locus coeruleus. This cascade would result in vigilance stabilization and delayed improvements in ADHD symptoms. However, in the current study, no evidence was found for this hypothesis, as we demonstrated comparable improvements sleep quality for all interventions **(chapter 4)**. According to other predictions of the model, delayed effects of neurofeedback should also be expressed in reduced frontal theta and alpha power. In an attempt to provide a definite answer to the question of whether neurofeedback induces specific neurological effects in children with ADHD, we explored EEG power spectra six months after the intervention

ended **(chapter 5)**. The findings at follow-up showed no differences between intervention groups on any of the power spectra, even when analyses adjusted for medication effects. There was also no significant relationship between the EEG power spectra changes and changes in behavioral outcomes from post-intervention to follow-up in the neurofeedback group, although significant associations between changes in behavioral and neurophysiological measures were found for children in both the stimulant medication and semi-active control groups. All in all, we found no specific effect for neurofeedback.

Instrumental learning

During neurofeedback, the patient is thought to learn to modify brain activity using visual and auditory feedback based on EEG activity. By training the patient to adapt brain activity using real-time feedback, neurofeedback aims to teach how specific cortical frequencies can be controlled. However, instrumental learning, the ability to change behavior in response to feedback, is thought to be impaired in children with ADHD.[12,13,27,28] Neurobiological models of ADHD suggest a deficiency in reinforcement learning due to altered levels and/or activity of striatal dopamine.[12,13,27,28] Although, these models differ in level of explanation,[29] they agree on the prediction that children with ADHD show poor reinforcement learning compared to controls, particularly when reinforcement is not delivered consistently.[12,13,27,28] The feedback provided through an EEG-driven computer might not always appear to be consistent for the participant. Therefore, it is important to explore learning from feedback in ADHD. In **chapter 6** of this thesis, we explored feedback learning using consistent (100% valid feedback) and probabilistic (85% or 70% valid feedback) feedback conditions in children with ADHD. Findings indicated that children with ADHD did have more difficulty learning from feedback than TD children. However, although children with ADHD showed initial learning problems, they were able to increase their performance in a similar manner compared to TD children. These findings were obtained both with feedback delivered consistent and probabilistic. In addition, we found that children with ADHD showed poorer generalization of what was learned compared to TD children, however, effects were small.

Previously, and in line with our results on feedback learning, our group found that children with ADHD who participated in the neurofeedback group were able to gain control over their EEG states during neurofeedback.[25] However, learning effects in theta and beta frequency bands were not significantly related to symptom improvement in children with ADHD. These findings might suggest that there is an insufficient transfer of learned skills to daily functioning. The importance

of the latter has already been emphasized.[24,30] In the current neurofeedback intervention study, we successfully implemented transfer trails and transfer cards. However, these additional remedies did not lead to the desired results of improved symptoms of ADHD.

Strengths and limitations of the study

The present study has a number of strengths, as well as some limitations. It is the first to compare behavioral effects of neurofeedback, optimally titrated stimulant medication, and a semi-active control condition (physical activity), in children diagnosed with ADHD. As far as we know, it is also the first to explore long-term effects of neurofeedback on EEG power spectra in children with ADHD. The thesis thus makes a contribution to knowledge in the field.

A particular strength of the research design was the achievement of large randomized intervention groups, with no baseline group differences on behavioral and neurocognitive outcome measures at pre-intervention, and low attrition rates at both post-intervention and follow-up. A variety of measures were used to assess the efficacy of neurofeedback in children with ADHD, and follow-up measures were included to assess possible long-term effects. The design included a semi-active control group to account for non-specific treatment effects, such as the impact of increased parental attention, and a medication control group allowed us to assess whether neurofeedback could provide a viable stand-alone alternative to stimulant treatment. Sensitivity analyses were conducted to control for stimulant medication use during the naturalistic follow-up assessment and its possible impact on outcome measures.

Nevertheless, there are also some limitations that should be noted. First, the theta/beta neurofeedback protocol used in this study may not be the best training protocol to use with children with ADHD. Other types of neurofeedback training such as frequency training or slow cortical potential (SCP) neurofeedback training might prove more effective. Currently, however, there is insufficient evidence to draw clear conclusions about this.[19] Second, our study used physical activity as a semi-active control condition where the frequency and intensity of the activity sessions were similar to the neurofeedback intervention. A review by Halperin, Berwid, and O'Neill[31] concluded that relatively intense physical activity can have positive effects on children's ADHD-related behaviors. It could therefore be argued that our semi-active control condition might have exerted beneficial effects on both behavioral and neurocognitive functioning of our participants, and thus might not have been the optimal comparison condition. However, children in the physical activity intervention received only two-minute bursts of physical activity during a time period of just 20 minutes. This is far less than the recommendations on physical activity found to be

beneficial in the literature.[31] It therefore seems unlikely that the physical activity protocol we used, exerted beneficial effects on neurocognitive functioning. More research on physical activity is necessary to substantiate its possible chronic effects on the problem behavior of children with ADHD.

The follow-up study described in **chapter 4** also suffered from a number of limitations, although these were addressed as far as possible. The long-term findings were obtained from a naturalistic, rather than an experimentally controlled, follow-up. Therefore, it is difficult to determine whether it was the interventions which improved long-term functioning at follow-up or whether some potentially unknown factors may have influenced our results. We do know that over a third (12 out of 32) of the children in the neurofeedback group had started medication treatment by the time of the six-month follow-up. However, we attempted to control for medication use at follow-up by performing sensitivity analyses, which did not reveal fundamentally altered results. Another issue was having different raters over time. Children in all three intervention groups were rated on a range of behavioural measures by both parents and teachers at six-month follow-up, but by the later point some of the children had different teachers. For this reason, Gevensleben et al.[32] and Steiner et al.[33] excluded teacher reports at follow-up. We reasoned that due to the randomized nature of the trial, results would be unlikely to be confounded. However, it does make the comparison of teacher reports over time less reliable and therefore results such as the teacher-rated improvement in the neurofeedback group at follow-up should be interpreted with caution.

Other studies have reported effects of stimulant medication on theta power,[34,35] alpha power[36,37] and beta power.[38] In **chapter 5** we found no such effects compared to the other interventions. A closer look at our power spectra data shows large variability in the EEG power spectra measures, especially for the alpha measures. This might have contributed to the fact that we did not find any evidence for stimulant mediated changes in the power spectra.

Finally, a potential limitation of **chapter 6** was that the children with ADHD had lower IQ scores compared to TD children, which may have influenced learning performance. However, we found performance in both groups to be independent of IQ, making it unlikely that the observed group differences might be related to the differences in IQ.

Implications and Future directions

Neurofeedback is an expensive and time-consuming alternative treatment for children with ADHD. This study was not able to demonstrate the effectiveness of theta/beta neurofeedback training in improving behavior and neurocognitive functioning in children with ADHD compared

to traditional treatment with stimulant medication, and therefore does not support its use as a stand-alone treatment.

Although children with ADHD seemed to profit more from medication than either neurofeedback or physical activity immediately post intervention, at the six-month follow-up children in the neurofeedback treatment group, and to a lesser extent the physical activity group, appeared to catch up with children originally randomized to receive medication. Six months after treatment ended, the behavioral and neurocognitive differences found post intervention came closer together. This could mean that medication gives an initial boost to the child and neurofeedback perhaps has a delayed effect, although this delayed effect may not be very strong as parent ratings in the neurofeedback and physical activity conditions did not differ at six-month follow-up.

Another direction for future research might be to undertake a well-designed study of the efficacy of physical activity as a treatment for children with ADHD. In our research, physical activity was used as a control group and the frequency and duration of physical activity sessions was matched to the frequency and duration of the neurofeedback sessions. This was substantially less than the recommendations on physical activity found in the literature.[31] Recently, however, a meta-analysis by Vyniauske et al.[39] on the impact of physical exercise on executive functioning and motor skills in children with ADHD indicated that longer exercise duration is associated with larger effect sizes. In addition, they found that exercise intensity, mean age of participants, or gender were not related to effect sizes. Nevertheless, more research is necessary as the studies used in this meta-analysis often had small samples, lack of control groups, and inconsistent reporting.

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Katleen Geladé was born on January 19th, 1984, in Diest, Belgium. When she was 17 she was determined to study psychology. In September 2002, she started her Bachelor in psychology at the University of Maastricht. To focus on her interest in psychiatry, she transferred to Leiden University in February 2006 to the attend a master in clinical psychology and child and adolescent psychology. In 2008, after doubting whether she wanted to work in the private sector or in psychiatric healthcare, she decided to join the Yulius Academy, the scientific knowledge centre within Yulius GGZ, an organisation with expertise in mental health care. In 2010, she started working as an external PhD student on the project 'Train your brain and exercise your heart? Advancing the treatment for attention deficit hyperactivity disorder (ADHD)' (ClinicalTrials.gov identifier: NCT01363544). After the manuscript was written in 2017, together with Lex den Doop, she developed, apart from a dizygotic twin, a digital twin. For more information about this information management tool please see: https://www.adigitaltwin.com.